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RNA TRANSCRIPTION/ SYNTHESIS

1. ANALYSIS OF TRANSCRIPTIONAL REGULATORY SIGNALS OF THE HSV THYMIDINE KINASE GENE: IDENTIFICATION OF AN UPSTREAM CONTROL REGION.

McKnight SL, Gavis ER, Kingsbury R
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Cell; 25(2):385-398 1981

We have identified a transcriptional control region of the herpes simplex virus tk gene. This finding results from in vivo transcription assays of specific deletion mutants constructed in vitro. A region located between 40 and 100 nucleotides upstream from the putative transcription start site of the tk gene can promote transcription by RNA polymerase Form II in the complete absence of the mRNA-coding component of the gene. When the region is deleted enzymatically from a 5' direction, accurate transcriptional expression is reduced by a factor of 50. The small remaining level of accurate transcription is eliminated by deletion of sequences from 32 to 16 nucleotides upstream from the structural gene. It appears that the

HE 20.3173/2:

sequences between 16 and 32 nucleotides upstream from the 5' terminus of the tk gene are required to specify the exact start site of transcription. Control of both the efficiency of transcription and rough specification of the position of initiation, however, depends on sequences 40-100 nucleotides upstream from the tk structural gene. (Author abstract) (49 Refs)

2. TRANSCRIPTION OF GLOBIN GENES IN MURINE ERYTHROLEUKEMIC CELL CHROMATIN BY RNA POLYMERASE II FROM MOUSE CELLS.

Nose K, Tanaka A, Okamoto H

Dept. Biochemistry, Toyoma Medical and Pharmaceutical Univ. Sch. Medicine, Sugitani, Toyama 930-01, Japan

J Biochem (Tokyo); 90(1):103-111 1981

RNA polymerase II was purified from mouse Ehrlich ascites tumor cells, and was used to transcribe chromatin from Friend leukemic cells at various stages of induction. The transcription was entirely dependent on exogenous RNA polymerase, and was inhibited by actinomycin D, or a low dose of alpha-amanitin. Globin-specific sequences of the transcripts were determined by hybridization of 3H-labeled transcripts with plasmid DNA immobilized on filters. When chromatin from uninduced cells was used, less than 0.01% of the total radioactivity was retained on the globin DNA-filters, whereas about 0.05% was retained when chromatin was made from induced cells. This value was about one-ninth of the content of cytoplasmic globin mRNA which was pulse-labeled in induced cells. The transcription of whole chromatin or globin genes in chromatin was inhibited almost completely by a rifampicin derivative, but in the case of chromatin, both sense and anti-sense strands of globin genes were transcribed. From these results, it is suggested that isolated chromatin retains some native conformation but is transcribed aberrantly. (Author abstract) (37 Refs)

3. ANTIPROLIFERATIVE EFFECTS OF RETINOIDS RELATED TO THE CELL CYCLE-SPECIFIC INHIBITION OF ORNITHINE DECARBOXYLASE.

Russell DH, Haddox MK

Dept. Pharmacology, Univ. Arizona Coll. Medicine, Tucson, AZ, 85724

Ann NY Acad Sci; 359:281-297 1981

A review is presented of the major experimental evidence obtained in Chinese hamster ovary (CHO) cells which supports the thesis that retinoid analogs affect the transcription of messenger RNA for ornithine decarboxylase (ODC) and thus arrest cells in G1 prior to the cell cycle-specific expression of ODC. Some of the areas explored include concentration-dependent inhibition of asynchronous CHO cell growth by retinoids; role of flow microfluorimetry in this inhibition; dose-dependent inhibition of ODC induction during G1 progression; lack of effect of retinol on activation of cyclic AMP-dependent protein kinase during G1; effect of RNA and protein synthesis in synchronized CHO cells; ODC expression after retinol block by actinomycin D; effect of retinol on other parameters of polyamine biosynthesis and accumulation and implications of retinol studies of synchronized CHO cells. Retinoids only inhibit the induction of ODC activity during the first 2-3 hr of G1 progression. It is postulated that ODC is a requirement for G1 progression and the antiproliferative properties of retinoids are related to the specific ability to inhibit this expression. Since retinoids do not markedly alter the rate of protein synthesis, their ability to inhibit ODC may be related to their ability to inhibit messenger RNA synthesis for ODC. (150 Refs)

4. REPAIR OF LESIONS WHICH CAUSE PREMATURE TERMINATION OF TRANSCRIPTION IN CHICKEN EMBRYO CELLS IRRADIATED WITH ULTRAVIOLET LIGHT.

Hackett PB, Varmus HE, BishopJM

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Virology; 112(2):752-756 1981

The dose-response curves for the synthesis of rRNA and avian sarcoma virus mRNA, after irradiation of virus-infected chicken embryo fibroblast cells, have shoulders. We tested the hypothesis that the shoulders were the result of dark repair of transcription-terminating lesions after irradiation by measuring the amounts of rRNA synthesized at various times after the uv dose was applied. Our data support the hypothesis and indicate that the rate of repair in transcribed genes of chicken cells is about one or two lesions removed per 10(6) base pairs of DNA per min during the first 3 hr after irradiation. (Author abstract) (17 Refs)

5. MODULATION OF 5-FLUOROURACIL (FURA) METABOLISM AND TOXICITY VIA ESTROGEN RECEPTOR (ER) (MEETING ABSTRACT).

Benz C, Cadman E

Yale University School of Medicine, New Haven, CT, 06510

4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

Hormonal modulation via ER is effective therapy in 50% of women with advanced breast cancer, most of whom will also be treated with FUra at some later time. Nuclear and cytoplasmic estrogen receptors (ERn and ERc) represent biological markers in malignancy that can be exploited in designing optimal chemo-hormonal therapy for human breast cancer. We have shown in an ERn+ (greater than 200fmol/mg DNA) human breast carcinoma cell line, 47-DN, that FUra metabolism and its modulation by methotrexate (MTX) can be altered by interferring with receptor-mediated biochemical events. The toxic 5-fluorouracil (FUra) metabolites, fluorodeoxyuridylate (FdUMP) (which inhibits DNA synthesis in S phase) and 5-Fluorouridine triphosphate (FUTP) (which incorporates into RNA in G1 phase) are biochemically quantitated; and FUra cytotoxicity is measured by a cloning assay. Flow cytofluorometry shows that greater than or equal to 24 hr of hormone deprivation, exposure to MTX or the antiestrogen Tamoxifen (TAM), all reduce S phase cells and increase G1 cells; ho wever the effects of these 3 pretreatments on FUra metabolism and toxicity in 47-DN are completely different. MTX pretreatment increases FUra metabolism and toxicity greater than or equal to 300%. Depriving 47-DN of insulin and estradiol reduces cellular growth rate, FUra phosphorylation and RNA incorporation greater than or equal to 50%, but does not impair toxicity. Exposure to TAM (greater than or equal to 1uM) reduces the rate of intracellular FUra accumulation but increases pools of FUTP. Growth inhibitory concentrations of TAM produce synergistic toxicity in combination with FUra or sequenced MTX-FUra, an example of 'complementary inhibition.' TAM, by binding to unoccupied ERn and altering receptor processing on DNA template, appears to selectively direct FUra entry into RNA, synergistically enhancing FUra toxicity. Perhaps these basic laboratory studies will provide the rationale for clinical trials selectively combining chemo-hormonal therapy in breast cancer. (no Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

6. THETA POLYPEPTIDE PHENOTYPES OF LYMPHOID AND MYELOID CELL LINES CONTAINING RNA TRANSCRIPTS OF THE IMMUNOGLOBULIN CTHETA GENE.

Walker ID, Harris AW
The Walter and Eliza Hall Inst. Medical Res., Victoria 3050, Australia
J Immunol; 127(2):561-566 1981

We have examined whether polyadenylated-RNA molecules encoded by the immunoglobulin Cmu gene (Cu RNA) that have recently been shown to occur in mouse T lymphoma, myeloid tumor, and pre-B lymphoma cell lines are translated. Three T lymphoma, one myeloid tumor, and four Abelson lymphoma cell lines, all known to contain Cu RNA molecules, were examined for evidence of synthesis of mu polypeptides using radioimmunoassay, biosynthetic labeling, and immunoprecipitation techniques. No mu polypeptides were detected in any of the T lymphoma or myeloid cell lines, although mu-chains were readily detected in two B lymphoma lines known to contain small amounts of mu mRNA. Detection failure is unlikely to be the result of assay insensitivity and was not caused by lack of an appropriate antiserum reactivity or a requirement of mu-chains to be associated with immunoglobulin light chains. Proteolytic activity that might degrade newly synthesized mu polypeptides in these cell lines was not detected. In three of the four Abelson lymphoma cell lines containing Cu RNA, corresponding polypeptides were absent, although in the fourth they were easily detected, indicating that transcription of the Cu gene is not the sole determinant of whether a cell will synthesize the corresponding polypeptide. The parallel between the Cu RNA+, mu polypeptide- Abelson cell lines and the T lymphoma cell lines suggests that the onset of Cu transcription may occur in both T and B lineages before translational competence is acquired. (Author abstract) (35 Refs)

7. MOLECULAR ANALYSIS OF IMMUNOGLOBULIN GENE VARIANTS.

Choi EM
University of California, Los Angeles, CA
Diss Abstr Int (B); 42(1):69-B 1981

MPC-11 mouse myeloma cells synthesized a normal kappa (k) light chain immunoglobulin and a variant k light chain fragment. The k fragment contains a hydrophobic precursor region joined directly to the k constant region (Ck) but lacks a variable region. The precursor region sequence of the k fragment is different from that of the full-length light chain. The full-length light chain and k fragment are encoded by separate messenger RNA (mRNA) species. Investigations on MPC-11 cells were undertaken in order to understand how the abnormal k fragment mRNA was generated. It is shown that the k fragment mRNA is formed from an aberrantly rearranged immunoglobulin gene through an abnormal RNA splicing event. (no Refs)

8. ADMINISTRATION OF 3-METHYLCHOLANTHRENE TO RATS INCREASES THE SPECIFIC HYBRIDIZABLE MRNA CODING FOR CYTOCHROME P-450C.

Bresnick E, Brosseau M, Levin W, Reik L, Ryan DE, Thomas PE
Dept. Biochemistry, Univ. Vermont Coll. Medicine, Burlington, VT, 05405
Proc Natl Acad Sci USA; 78(7,part2):4083-4087 1981

Poly(A)+-RNA obtained from the livers of 3-methylcholanthrene (3MC)-treated rats was translated into cytochrome P-450c in a cell-free reticulocyte system. In this translational system, no precursor cytochrome P-450c was observed. The mRNA responsible for the synthesis of this cytochrome was isolated by immunoprecipitation of liver polyribosomes obtained at 15 hr after 3MC treatment, and a cDNA was constructed by the reverse transcriptase reaction. The cDNA was further purified by hybridizing at a high Rot (product of RNA concentration and incubation time) to poly(A)+-RNA isolated from control rat liver, and the nonhybridized, single-stranded cDNA was isolated by hydroxylapatite chromatography. This cDNA(P-450c)was employed in hybridization reactions with poly(A)+-RNA isolated from the livers of rats treated with 3MC for various times. These studies indicated a maximal induction of mRNA(P-450c) at about 15 hr after 3MC injection, although levels of this mRNA were significantly increased by 7 hr. The mRNA(P-450c) concentration had diminished by 24 hr but remained higher than control levels for at least 48 hr. These studies establish an effect of MC upon the accumulation of mRNA(P-450c) in rat liver. (Author abstract) (41 Refs)

9. THE 28 S GENOMIC RNA OF AVIAN SARCOMA VIRUS PRCII CODES FOR THE TRANSFORMATION-SPECIFIC POLYPROTEIN P105.

DeLamarter JF, Neil JC, Ghysdael J, Vogt PK
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Virology; 112(2):757-761 1981

We have characterized the genomic RNA of the defective avian sarcoma virus PRCII . Replicating virus which consists of transforming PRCII and a nontransforming but replication-competent helper, PRCII-AV, contains two RNA species. One is identical in size to the 35 S genome of avian leukosis helper viruses. The second component migrates slightly faster than 28 S ribosomal RNA in polyacrylamide gel electrophoresis but cosediments with this RNA in sucrose gradients. In vitro translation across a gradient of velocity-sedimented poly(A)-containing PRCII virion RNA yielded three major proteins. The virion protein precursors Pr76gag and Pr180gag-pol were translated from 35 S RNA, while the transformation-specific polyprotein P105 was translated from 28 S RNA. P105 may be the only protein coded for by the PRCII genome, although this product would not exhaust the coding capacity of 28 S RNA. Whether translated in vitro or immunoprecipitated from transformed cells, P105 was essentially identical as demonstrated by comparative peptide maps. (Author abstract) (25 Refs)

STRUCTURE AND LEVELS OF TRANSFER RNA

10. THE SEQUENCE OF MITOCHONDRIAL ARGININE TRNA (ANTICODON UCG) FROM A TRANSPLANTABLE RAT TUMOR, MORRIS HEPATOMA 5123D.

Agrawal HP, Gupta RC, Randerath K, Randerath E
Dept. Pharmacology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030
FEBS Lett; 130(2):287-290 1981

To isolate transferRNA-ArgUCG (tRNA Arg), total nucleic acids were extracted in the presence of phenol from Morris hepatoma 5123D mitochondria (mt) pellets and fractionated on diethylaminoethyl-cellulose to obtain crude tRNA. The tRNA was purified on three successive polyacrylamide gels; tRNA Arg was extracted after methylene blue staining and its sequence determined by a thin layer readout technique. 32P-labeled RNA fragments were resolved on gels and their termini analyzed in two complementary systems. When compared with eukaryotic cytoplasmic and prokaryotic tRNAs, the hepatoma mt tRNA Arg exhibited many unusual features, such as predominance of U (36.7%) and A (42.3%) over C (11.3%) and G (9.9%), the presence of m1A in position 9, lack of -GG- in loop I, lack of -UUCPu-(TpsiCPu-) in loop IV, small size of these loops, and lack of the constant G.C base pair adjacent to loop IV. tRNA Arg exhibited approx 86% sequence homology with the DNA-derived putative sequence of human placenta mt tRNA Arg. Differences, including transitions and transversions, were found in acceptor stem and D-stem close to the center of the cloverleaf structure and in loops I, III, and IV. (26 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

11. A MOUSE CELL LINE, WHICH IS UNPROTECTED BY INTERFERON AGAINST LYTIC VIRUS INFECTION, LACKS RIBONUCLEASE F ACTIVITY.

Epstein DA, Czarniecki W, Jacobsen H, Friedman RM, Panet A
Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, 9000 Rockville Pike, Bethesda, MD, 20205
Eur J Biochem; 118(1):9-15 1981

A mouse cell line, NIH 3T3, does not respond to some of the activities of interferon. Even after treatment with high concentrations of interferon the replication of lytic viruses, such as encephalomyocarditis virus (EMCV) and vesicular stomatitis virus (VSV) is not inhibited in these cells. In contrast, interferon treatment of these same cells results in the inhibition of Moloney murine leukemia virus (MMuLV) production. We have analyzed enzymatic pathways which are induced by interferon in these cells. After interferon treatment, the level of the (2'-5')oligoadenylate [(2'-5')An] synthetase activity and the phosphorylation of the 67,000-dalton protein (P1) are enhanced in NIH 3T3 cells to approx the same level as interferon-sensitive mouse L-cells. Moreover, NIH 3T3 and L-cells contain approx the same levels of enzymes which inactivate (2'-5')An. Both exogenously added (2'-5')A3 or double-stranded RNA (dsRNA) failed to inhibit protein synthesis in NIH 3T3 extracts even though they were potent inhibitors of L-cell extract-directed protein synthesis. Direct measurements of the (2'-5')An-dependent ribonuclease F (RNase F) failed to detect such activity in NIH 3T3 cells. Our results, therefore, suggest that the presence of RNase F activity is necessary for the interferon-induced antiviral activity against EMCV and against VSV. The induction of protein kinase activity by interferon treatment of NIH 3T3 cells appears to have no direct effect on EMCV and VSV replication. (Author abstract) (44 Refs)

12. NUCLEAR DNA-DEPENDENT RNA POLYMERASES FROM MORRIS HEPATOMAS AND RAT LIVER: MECHANISMS FOR INCREASED ACTIVITY OF POLYMERASE I IN TUMOR 3924A.

Duceman BW
The Pennsylvania State University, University Park, PA
Diss Abstr Int (B); 42(1):165-B 1981

DNA-dependent RNA polymerases were solubilized from homogenates of resting or regenerating rat livers and from a series of four Morris hepatomas (designated as tumors 5123D, 7800, 7777, 3924A). Following extraction, RNA polymerases I, II, and III were resolved by diethylaminoethyl-Sephadex column chromatography and the total activity of each polymerase from the respective tissues was determined. When compared with resting liver values, the tumors exhibited a characteristic pattern of enzyme activities in which RNA polymerase I, but not II, was elevated. The greatest increase in polymerase I (3-fold per mg DNA) was associated with the fastest growing hepatomas, 7777 and 3924A. Similarly, enhanced polymerase III activity (2-fold per mg DNA) was confined to the more rapidly proliferating tumors. In contrast, all classes of RNA polymerase were increased during liver regeneration (18 hr after partial hepatectomy). The mechanisms underlying the increased synthesis of RNA in vitro by bound polymerase I from tumor 3924A were elucidated by product analysis. (no Refs)

13. MECHANISM OF INTERFERON ACTION. INHIBITION OF PPPA(2'P5'A)N-DEPENDENT RIBONUCLEASE ACTIVITY IN MICROCOCCAL NUCLEASE-TREATED MOUSE L CELL-FREE EXTRACTS.

Miyamoto NG, Samuel CE
Section Biochemistry and Molecular Biology, Dept. Biological Sciences, Univ. California, Santa Barbara, CA, 93106
Biochem Biophys Res Commun; 101(2):680-688 1981

The molecular basis by which the pppA(2'p5'A)n-dependent ribonuclease activity is blocked in micrococcal nuclease-treated as compared to nonpreincubated cell-free extracts prepared from interferon (IF)-treated mouse L cells was investigated. The micrococcal nuclease was purified from the Foggi strain of Staphylococcus aureus. Nonpreincubated and micrococcal nuclease-treated cell-free S-10 extracts were prepared from mouse L fibroblast cells grown in suspension culture. The mouse L cell-free extracts were supplemented with 2'-deoxythymidine-3',5'-diphosphate (pTp) and ethyleneglycol-bis(beta-aminoethyl ether)-N,N'-tetraacetic acid (EGTA) to catalyze the 2'-5'-oligo A tetramer enhanced degradation of reovirus [3H] messenger (m)RNA. Results indicated that (1) digestion of endogenous cellular RNA by the micrococcal nuclease during the preparation of the mRNA-dependent protein synthesizing system is required to establish the apparent inhibition of the 2',5'-oligo A-dependent ribonuclease, and (2) neither pTp nor EGTA directly affected the activity of either the 2',5'-oligo A synthetase or the 2',5'-oligo A-dependent ribonuclease in mouse L cells. (18 Refs)

14. METABOLISM OF PYRIMIDINE NUCLEOTIDES IN VARIOUS TISSUES AND TUMOR CELLS FROM RODENTS.

Ikenaka K, Fukushima M, Nakamura H, Okamoto M, Shirasaka T, Fujii S
Div. Regulation Macromolecular Function, Inst. Protein Res., Osaka Univ., 5311 Yamada-kami, Suita 565, Japan
Gan; 72(4):590-597 1981

The metabolism of pyrimidine nucleotides in various tissues and tumor cells of rodents were investigated. Ribonucleoside diphosphate reductase, thymidine monophosphate kinase and DNA polymerase (alpha, beta) were specifically localized in tumor cells, ie, the activities of these enzymes in tumor cells were at least three times higher than those in normal tissues, including rapidly growing tissues, such as bone marrow, thymus, and spleen. The activities of deoxycytidine monophosphate deaminase and all the nucleoside kinases were high not only in tumor cells, but also in rapidly growing normal tissues, so that these enzymes are unsuitable as targets for cancer chemotherapy. The tissue distribution of other enzymes, including orotate phosphoribosyltransferases, cytidine triphosphate synthetase, thymidine monophosphate synthase, nucleoside phosphorylases and cytidine deaminase had no relation with the cell growth rate. AH130 tumor cells and the thymus showed specific increases in the activities of enzymes involved in de novo DNA synthesis. In contrast, Yoshida sarcoma and bone marrow showed high activities of enzymes in the salvage pathway of DNA synthesis, which suggested that the two tumors have different patterns of nucleotide metabolism. (Author abstract) (19 Refs)

15. NON-SPECIFICITY OF ELEVATED SERUM RIBONUCLEASE AS A PANCREATIC TUMOUR MARKER.

Isaacs P
Gastroenterology Unit, Guy's Hosp., London SE1 9RT, England
Digestion; 22(2):101-107 1981

Differences in heat stability of human pancreatic ribonuclease and serum ribonuclease were abolished by aprotinin, suggesting that the pancreatic enzyme was similar to the serum enzyme, but was being destroyed by proteases. Serum ribonuclease levels in normal subjects correlated with age but were unaffected by meal ingestion. Serum ribonuclease was not found to be useful in the detection of pancreatic cancer and was more frequently abnormal in patients with other solid tumors or renal failure. (Author abstract) (26 Refs)

OTHER RELATED STUDIES

16. IN VIVO AND IN VITRO EFFECTS OF XENOGENEIC IMMUNE RIBONUCLEIC ACID IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA: A PHASE I STUDY.

Richie JP, Wang BS, Steele GD, Wilson RE, Mannick JA, Catalona WJ
Dept. Surgery/Urology, Peter Bent Brigham Hosp, Harvard Medical Sch., Boston, MA
J Urol; 126(1):24-28 1981

Based upon demonstration in our laboratory of repeated prevention of pulmonary metastases by adjuvant immune RNA in animal preparations, xenogeneic immune RNA was given in a phase I study to patients with advanced renal cell carcinoma. Six patients were treated with iv infusions of autologous lymphocytes incubated in vitro with immune RNA extracted from splenocytes of guinea pigs immunized with the patient's own tumor. Serial peripheral blood lymphocytes were obtained during and after each treatment with immune RNA for in vitro evaluation of cell-mediated cytolysis by 51Cr release assay and 125-I iododeoxyuridine assay against allogeneic renal cell carcinoma targets and melanoma targets. Neither toxicity nor enhancement of tumor growth was observed. All patients demonstrated significantly increased cell-mediated cytolysis against allogeneic renal cell carcinoma targets but no change against melanoma targets. Increased cell-mediated cytolysis could be demonstrated in individual blood samples after incubation with immune RNA. Further, progressive in vivo effect was demonstrated in in vitro assay of serial peripheral blood lymphocytes before each successive exposure to immune RNA. Increased cell-mediated cytolysis persisted in peripheral blood lymphocytes up to 9 mo after therapy. Although without controls one patient had complete response and two patients had partial responses (8 to 18 mo). Two patients had stabilization of the disease for 3 to 4 mo and one patient had progression of cerebral metastases. One patient is alive 24 mo after therapy. These results would favor the institution of a randomized prospective trial in patients with advanced renal cell carcinoma or lesser tumor burdens. (Author abstract) (25 Refs)

17. MORPHOLOGY OF NUCLEAR RIBONUCLEOPROTEINS IN THE EARLY PERIOD OF LIVER REGENERATION AFTER IRRADIATION.

Orkisz S, Bartel H
Dept. Histology and Embryology, Inst. Biology and Morphology, Medical Military Acad., Plac 9 Maja 1, PL-90-647 Lodz, Poland
Histochemistry; 71(4):629-634 1981

Ultracytochemical studies of rat hepatocyte nuclei were conducted in order to evaluate the distribution and behavior of nuclear ribonucleoproteins in the regenerating liver following irradiation. After the stimulus of hepatectomy or gamma radiation (650 rads), perichromatin fibrils formed a marked condensation sphere around the condensed chromatin areas. Ionizing radiation increased perichromatin granule (PG) number maximally after 2/3 liver resection. The large PG concentration 48 hr after hepatectomy could be the morphological expression of transport delay of messenger RNA to cytoplasm under the influence of gamma radiation. (30 Refs)

18. INDIRECT ALKYLATION OF CBA MOUSE LIVER DNA AND RNA BY HYDRAZINE IN VIVO. A POSSIBLE MECHANISM OF ACTION AS A CARCINOGEN.

Quintero-Ruiz A, Paz-Neri LL, Villa-Trevino S
(c/o Villa-Trevino) Departamento Investigacion, Division de Estudios, Superiores de la Facultad Medicina Universidad Autonoma de Chihuahua, Apart Postal 1506 Sucursal 'C' Chihuahua, Chihuahua, Mexico
JNCI; 67(3):613-618 1981

Treatment of inbred CBA mice with hydrazine sulfate, a liver carcinogen, plus [14C]formate or L-[methyl-14C]-methionine as a source of 'C1' units, produced [14C]7-methyl-guanine (7-MG) in liver DNA and RNA. This methylated guanine was identified by its chromatographic characteristics in three different systems: on Sephadex G10, on Dowex 50, and by paper co-chromatography with authentic 7-MG. Mice that received [14C]formate alone showed no 7-MG in their DNA or RNA. In addition, mice treated with L-[methyl-14C]methionine alone showed no 7-MG in their DNA. These results suggest that 'indirect' alkylation of nucleic acids is a mechanism of cancer initiation by hydrazine. (Author abstract) (20 Refs)

19. CHARACTERIZATION AND SUBCELLULAR LOCALIZATION OF 7-8 S RNAS OF NOVIKOFF HEPATOMA.

Reddy R, Li WY, Henning D, Choi YC, Nohga K, Busch H
Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
J Biol Chem; 256(16):8452-8457 1981

Five distinct 7-8 S small nuclear RNAs from Novikoff hepatoma were characterized by fingerprinting and their subcellular localization. Two of these RNAs (7-1 and 7-2) were not found earlier. A 7 S RNA previously reported to be localized to cytoplasm was found in nuclei in amounts of 30-50% of the total. RNA 7-3 was nucleoplasmic and was different from 7 S RNA. Several RNAs, 7-1, 7-2, 8 A, and 8 B, were found in nucleoli. The RNAs 7-1, 8 A, and 8 B were released from nucleolar 28 S RNA extracted at 25 C by heating the RNA to 65 C. The T1 RNase fingerprints of RNAs 8 A and 8 B were very similar. The similarities of the fingerprints of the 7 S RNAs of HeLa and Novikoff hepatoma cells support earlier suggestions that these RNAs are conserved through evolution. (Author abstract) (37 Refs)

20. MODE OF ACTION OF GCE: AN ACTIVE ANTICANCER PRINCIPLE ISOLATED FROM AN INDIGENOUS PLANT GYMNOSPORIA ROTHIANA LAWS.

Chapekar MS, Sahasrabudhe MB
Dept. Pathology, Arlington Hosp., George Mason Drive, Arlington, VA
Indian J Exp Biol; 19(4):333-336 1981

The mechanism of action of chloroform ether extract (GCE), obtained from the roots of the plant Gymnosporia rothiana Laws, on L-1210 and P-388 transplantable tumors from BDF1 mice was examined. The viability of P-388 cells following treatment with 1 and 10 ug GCE was reduced to 68% and 58%, respectively, after 6 hr of drug exposure. After 4 and 6 hr of exposure to 100 ug GCE, the viability of P-388 cells was reduced to 58% and 27%, respectively. The viability of L-1210 cells was reduced to 40% and 0% after 6 hr of exposure to doses of 50 and 100 ug of GCE, respectively. In vivo animal bioassay studies indicated that GCE killed 90% and 98% of the cells after 2 and 6 hr in vitro exposures, respectively, of 1 x 10(6) cells to 100 ug GCE. For 10 ug of GCE, inhibition of DNA, RNA, and protein biosynthesis was 17%, 19%, and 50%, respectively. At 80 ug GCE, inhibition of the macromolecules was about 70%. Administration of 25 ug/kg GCE/mouse to L-1210 tumor bearing mice led to max protein synthesis inhibition after 12 hr of GCE treatment, max RNA synthesis inhibition after 24 hr, and max DNA synthesis inhibition after 36 hr. (11 Refs)

21. PHYSIOLOGICAL ADAPTATION AT THE MOLECULAR LEVEL: THE FRONTIER WHERE RESEARCH ON DIFFERENTIATION AND MALIGNANCY MEET.

Potter VR
McArdle Memorial Lab., Univ. Wisconsion Medical Sch., Madison, WI, 53706
Perspect Biol Med; 24(4):525-542 1981

Research on physiological adaptation that combines the holistic and reductionist approaches was believed to be the key to understanding differentiation and malignancy. The concept that the most significant aspect of the genetic program for differentiation is the development of a whole organism capable of physiological adaptation was proposed. In other words, the capability is a condition in which every cell lineage contains a few or many cells that are capable of fairly rapid shifts in th amount and activity of the enzymes, transport mechanisms, receptors, and proliferative essentials, all designed to make the total organism physiologically adapted to a changing environment. Normal differentiation was considered to be a process that is directed toward competence for physiological adaptation, while cancer cells fail to carry out the program. It was suggested that a change in the net rate of synthesis of one or more types of messenger RNA together with a change in the corresponding enzyme amount and activity be considered to represent physiological adaptation. Similarly, the ability to regulate cell division, was thought to be an important aspect of physiological adaptation as related to differentiation and malignancy; however regulation of cell division is the sixth line of defense in the hierarchy of six cellular defense lines available during physiological adaptation at the molecular level. (43 Refs)

22. SYNERGISTIC EFFECT OF 5-FLUOROURACIL AND N-(PHOSPHONACETYL)-L-ASPARTATE ON CELL GROWTH AND RIBONUCLEIC ACID SYNTHESIS IN A HUMAN MAMMARY CARCINOMA.

Ardalan B, Glazer RI, Kensler TW, Jayaram HN, Pham TV, MacDonald JS, Cooney DA
Div. Medical Oncology, City of Hope Natl. Medical Center, 1500 East Duarte Road, Duarte, CA, 91010
Biochem Pharmacol; 30(15):2045-2049 1981

The biological effects of N-(phosphonacetyl)-L-aspartate (PALA) and 5-fluorouracil (5-FU) were examined singly, and in combination, on the growth of a human mammary carcinoma (MDA) cell line in culture. All combinations of 5-FU (2.5 x 10(-7) to 1.5 x 10(-5) M) and PALA (6.0 x 10(-5) to 3.6 x 10(-3) M) resulted in synergistic inhibition of cell growth as revealed by a 50% isobologram. To examine the biochemical basis for the synergism, measurements of the incorporation of [3H]-5-FU into total non-poly(A)- and poly(A)-RNA, and of the simultaneous incorporation of [14C]deoxyguanosine and [3H]deoxyuridine into DNA, were determined. The combination of 3.7 x 10(-5) M PALA and 1 x 10(-6) M 5-FU produced 65-85% inhibition of cell growth after continuous treatment for 1-3 days. Treatment of the cells for 3 or 24 hr with the same drug regimen produced approx a 170% increase in the incorporation of 1 x 10(-6) M [3H]-5-FU into poly(A)RNA in comparison to [3H]-5-FU treatment alone; exposure for 24 hr to 3.7 x 10(-5) M PALA and 1 x 10(-6) M [3H]-5-FU resulted in a 285% increase in the incorporation of [3H]-5-FU into non-poly(A)RNA. The incorporation of either [14C]deoxyguanosine or [3H]deoxyuridine into DNA was not inhibited by this drug regimen; however, the incorporation of [3H]deoxyuridine into DNA was elevated significantly upon 12 or 24 hr of exposure to PALA alone. PALA and 5-FU treatment resulted in a 75% reduction in the concentration of UTP and no change in the concentration of 5-fluorouridine-5'-triphosphate (5-FUTP) versus 5-FU treatment alone. Thus, the proportion of 5-FUTP in the total 5-FUTP + UTP pool was enhanced more than three-fold by the combination regimen. These results indicate that the synergistic effect of the combination of PALA and 5-FU on the growth of MDA cells correlates with an increased proportion of 5-FUTP in the pyrimidine nucleotide pool and, consequently, with an enhanced incorporation of 5-FU into RNA, but not with inhibition of DNA synthesis. (Author abstract) (25 Refs)

23. INHIBITION OF TUMOR GROWTH BY COMBINED TREATMENT WITH CYCLOPHOSPHAMIDE (CY) AND POLYADENYLIC AND POLYURIDYLIC ACID (POLY (A):POLY (U)) IN C3H MICE BEARING A TRANSPLANTABLE MAMMARY TUMOR (MEETING ABSTRACT).

Lacour F, Youn JK, Hue G
Institut Gustave-Roussy, 94800 Villejuif, France
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

The inhibition of tumor growth by CY administered sequentially in association with immunomodulators, POLY (A): POLY (U) or BCG, was studied in C3H mice bearing a transplantable syngeneic mammary tumor. A total of 212 mice were inoculated at Day 0 with 10(6) tumor cells. At Day 14 when their tumors attained palpable size, they received either 4 fortnightly inoculations of CY (90 mg/kg) alone or alternate weekly inoculations of the same doses of CY and POLY (A). POLY (U) (300 or 600 ug) or BCG (400 ug) during 8 consecutive wk. At Day 170, the following results were obtained. 1) Mice received either POLY (A): POLY (U) or BCG alone showed as rapid growth of tumor as observed in control untreated tumor bearers. 2) Mice received CY alone showed significantly delayed tumor growth and only 2 mice out of 34 (6%) were tumor free. 3) The most significant inhibitory effect was observed in mice received combined CY and POLY (A): POLY (U): 11 mice out of 44 (25%) were tumor free and tumor sizes of tumor bearers at Day 65 were less than half of those of mice receiving CY alone (mean diameter of 2.2 mm instead of 6.0 mm. 4) No such synergistic inhibitory effect was observed in mice that received combined CY and BCG. These results indicate that POLY (A): POLY (U) combined with a non toxic dose of cytostatic agent significantly improved the results obtained with the drug alone. (no Refs)

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RNA TRANSCRIPTION/ SYNTHESIS

1. ELEVATED TRANSCRIPTIONAL COMPLEXITY AND DECREASE IN ENZYMATIC DNA METHYLATION IN CELLS TREATED WITH L-ETHIONINE.

Boehm TL, Drahovsky D
(c/o Drahovsky) Zentrum der Biologischen Chemie, Universitat Frankfurt am Main, Theodor Stern-Kai 7, D-6000 Frankfurt am Main 70, W. Germany
Cancer Res; 41(10):4101-4106 1981

This paper analyzes the extent of enzymatic methylation of DNA in P815 cells cultured for several cell cycles in the presence of 1 mM L-ethionine by use of the bacterial restriction enzymes Hpall, Mspl, Hhal, Haell, and Aval. The results obtained suggest that the extent of methylation of DNA is decreased during L-ethionine treatment and that the degree of this inhibition varies among different methylation sites. The nucleotide sequence complexity of nuclear RNA in P815 cells was analyzed by excess hybridization with tracer amounts of nick-translated nonrepetitive P815 [3H]DNA sequences. About 6.2% of the nonrepet itive sequences form hybrids with nuclear RNA of control cells, whereas 8.8% are complementary to nuclear RNA from L-ethionine-treated cells. Thus, the de-

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crease in enzymatic DNA methylation correlates with the presence of new transcriptional products suggesting that this modification process inversely correlates with the initiation of transcription. (Author abstract) (45 Refs)

2. INTERACTION OF THE ANTITUMOR DRUG 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDIDE AND RELATED ACRIDINES WITH NUCLEIC ACIDS.

Wilson WR, Baguley BC, Wakelin LP, Waring MJ
Dept. Pathology and Cell Biology, Univ. Auckland Sch. Medicine, Private Bag, Auckland, New Zealand
Mol Pharmacol; 20(2):404-414 1981

The acridine antitumor drug 4'-(9-acridinylamino)methanesulfon-m-anisidide (m-AMSA) is known to be an inhibitor of nucleic acid synthesis. Correlation between m-AMSA (and other related acridine) binding to different nucleic acids (calf thymus) and biological activity and molecular structure were examined using equilibrium dialysis, spectrophotometry, and competition with ethidium. All three techniques indicated an intrinsic association constant of approx 1.5 x 10(5)/M at an ionic strength of 0.01. Increasing ionic strength depressed the association constant by a factor corresponding to that predicted for a monocationic ligand. Binding of m-AMSA was highly selective for native DNA; its affinity for heat-denatured DNA and ribosomal RNA was lower by factors of 5 and 25, respectively. All acridines examined discriminated in favor of DNA Among seven acridines tested, no simple correlation could be found between antitumor potency or selectivity and strength of DNA binding. Presence of an unsubstituted methanesulfonanilide ring did not interfere with binding to double stranded DNA, but addition of a methoxy substituent at the 3' ring position may sterically hinder intercalation of the acridine nucleus of the drug. (36 Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

3. TUMOR-SPECIFIC POLYADENYLATED RNA'S FROM 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS REVEALED THROUGH HYBRIDIZATION WITH FRACTIONATED SINGLE-COPY DNA.

Supowit SC, Rosen JM
Dept. Cell Biology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030
Cancer Res; 41(10):3827-3834 1981

Polyadenylated (poly(A)+) and nonpolyadenylated (poly(A)-) RNA fractions from primary, hormone-dependent, 7,12-dimethylbenz(a)anthracene-induced mammary tumors and normal rat mammary tissue were analyzed by molecular hybridization to determine if there is a unique class of 'tissue-specific' RNA sequences. Single-copy [3H]DNA was fractionated into probes which were either depleted of midpregnant RNA sequences or complementary to these same sequences. When these probes were annealed to homologous and heterologous poly(A)+ RNA's, distinct sets of single-copy sequences were found in the two pol y(A)+ RNA populations. The complexity of the 'tumor-specific' sequences was about 6.7 x 10(7) nucleotides (assuming asymmetrical transcription). Hybridization of the poly(A)- RNA fractions isolated from the 7,12-dimethylbenz(a)anthracene-induced tumors and the normal mammary gland to poly(A)- complementary DNA's revealed that both tissues appear to contain a class of poly(A)- RNA sequences which were distinct from the set of poly(A)+ RNA's. Both poly(A)- RNA fractions saturated at 3% when hybridized to single-copy [3H]DNA. However, approx 15 to 25% (minimum estimate) of the complexity of the poly(A)- RNA was contributed by contaminating poly(A)+ RNA sequences. Therefore, the actual complexity of the poly(A)- RNA fractions was 2.0 to 2.5% of the single-copy hybrid genome. Mixtures of these two RNA fractions also gave a saturation value of 3.0% when annealed to single-copy [3H]DNA. This indicated that most of the poly(A)- RNA's were similar in the neoplastic and normal mammary tissues. Although the majority of the infrequent RNA species are held in common between the two tissues, there is a distinct set of high-complexity poly(A)+ RNA sequences, presumably of nuclear origin, which is unique to the 7,12-dimethylbenz(a)anthracene-induced tumors. Whether these RNA's are processed and became functional messenger RNA's is not known. Presumably, they play a role in regulating the frequencies of the tissue-specific abundant and moderately abundant messenger RNA's and therefore provide one mechanism by which the concentration of specific proteins and ultimately the expression of the transformed phenotype may be regulated. (Author abstract) (40 Refs)

4. 5'-TERMINAL CAP STRUCTURES OF OLIGO(URIDYLIC ACID)-CONTAINING MESSENGER RIBONUCLEIC ACID FROM HELA CELLS: COMPARISON WITH OTHER RIBONUCLEIC ACID SUBPOPULATIONS.

Wallace JC, Wood WM, Edmonds M
Dept. Biological Sciences, Univ. Pittsburgh, Pittsburgh, PA, 15260
Biochemistry; 20(19):5364-5368 1981

The 5'-terminal cap structures of 32P-labeled oligo(uridylic acid)-containing messenger RNA [oligo(U+) mRNA] isolated from HeLa cell polyadenylated [poly(A+)] mRNA were analyzed and compared to those of the poly(A+) mRNA. A method employing P1 nuclease, alkaline phosphatase, and adsorption to activated charcóal showed that the types of cap core (m7 GpppXm) in oligo(U+) mRNA were essentially identical with those in poly(A+) mRNA. Analysis of RNase T2 digestion products of oligo(U+) mRNA demonstrated the presence of both cap 1 (m7GpppXmpYp) and cap 2 (m7GpppXmpYmpZp) in this subpopulation, confirming its cytoplasmic location. The base compositions of these two types of caps were different from each other and nonrandom but did not differ significantly between oligo(U+) and poly(A+) mRNA. The only observed difference between the mRNA populations was a higher ratio of cap 1 to cap 2 in the former. Possible implications of the se findings for the relationship between oligo(U+) mRNA and poly(A+) mRNA are discussed. (Author abstract) (14 Refs)

5. A METHOD FOR ISOLATION OF OLIGO(URIDYLIC ACID)-CONTAINING MESSENGER RIBONUCLEIC ACID FROM HELA CELLS.

Wood WM, Edmonds M
Dept. Biological Sciences, Univ. Pittsburgh, Pittsburgh, PA, 15260
Biochemistry; 20(19):5359-5364 1981

When cytoplasmic polyadenylated RNA [poly(A+) RNA] from HeLa cells was treated with ribonuclease H (RNase H) and oligodeoxythymidylate [oligo(dT)] to remove its 3'-poly(A) tail, an increased binding to poly(A)-agarose was observed. The bound material, which comprised 4-6% of the initial RNA, contained 65-80% of the oligo(uridylic acid)[oligo(U)] sequences generated by RNase T1 digestion. Oligo(U) isolated from the bound fraction was shown to be 83% U and to have a U/G ratio of 33. In contrast, oligo(U) from the unbound material was 77% U and had a U/G ratio of 13, suggesting that it is shorter and less U rich than the oligo(U) in the bound fraction. On sucrose gradients, oligo(U+) RNA consistently sedimented with a larger s value than oligo(U-) RNA. The oligo(U) content of oligo(U+) RNA suggests one oligo(U) tract of 33 nucleotides per RNA molecule of 2,000-3,000 residues. (Author abstract) (27 Refs)

6. GENERATION OF LONG MRNA FOR MEMBRANE IMMUNOGLOBULIN GAMMA2A CHAINS BY DIFFERENTIAL SPLICING.

Tyler BM, Cowman AF, Adams JM, Harris AW
The Walter and Eliza Hall Inst. Medical Res., PO Royal Melbourne Hosp., Victoria 3050, Australia
Nature; 293(5831):406-408 1981

The messenger RNA (mRNA) for the membrane IgG gamma2a chain of murine 2PK-3 B-lymphoma cells was identified by hybridization analysis. Polyadenylated RNA from 2PK-3 cells was fractionated by electrophoresis, then blot transferred and hybridized to Cgamma2a probes. Two gamma2a species were detected, approx 1.9 and 3.9 kilobases (kb) long. Analysis with a V-region probe indicated that the 3.9-kb species is the membrane gamma2a chain mRNA and the 1.9-kb species is the corresponding secreted-chain mRNA. The longer mRNA was spliced differently at the 3' end. It was generated by a splice that replaced the 100 base-pair secreted gamma2a 3'-untranslated region with a 2.1-kb sequence encoded 3' to the Cgamma2a gene. (25 Refs)

7. SYNTHESIS OF MRNA GLOBIN IN DISTURBANCES OF ERYTHROID CELL DIFFERENTIATION.

Peresleni TIu, Dvorkin GA
Inst. General Genetics, Moscow, USSR
Dokl Akad Nauk SSSR; 258(6):1492-1495 1981

Synthesis of globin messenger RNA (mRNA) was studied in a culture of erythroblasts transformed by Rauscher virus and in the spleen of mice with Rauscher erythroleukemia. Molecular hybridization of globin complementary DNA with RNA isolated from Rauscher erythroleukemia cells showed virtual absence of globin mRNA. (14 Refs) (In RUS)

8. DIFFERENCE IN GENETIC EXPRESSION BETWEEN NORMAL AND TRANSFORMED WI-38 CELLS.

Nose K, Okamoto H, Namba M
Dept. Biochemistry, Toyama Medical and Pharmaceutical Univ. Sch. Medicine, Sugitani, Toyama, Japan
Cell Struct Funct; 6(2):93-101 1981

In order to study transformation-specific gene expression, total poly(A)+RNA was extracted from normal WI-38 and Co60-irradiation-transformed WI-38 (CT-1) human diploid fibroblasts, complementary DNA (cDNA) against this RNA was prepared, and hybridization studies of these two nucleic acids were performed; also, radiolabeled proteins from the normal and transformed cells were prepared and examined by two-dimensional gel electrophoresis. Poly(A)+RNA sedimenting from 5S to 23S was hybridized to cDNA fractions greater than 150 bases (av size: 300 bases) in two combinations: homologous (both nucleic acids came from the same cell type) and heterologous (the RNA and DNA came from opposite cell types); considerable hybridization occurred in both cases, showing that there is extensive homology between the poly(A)+RNAs of normal and transformed cells. Approx 200 protein spots were examined electrophoretically from both cell types, first by isoelectrofocusing and then by sodium dodecyl sulfate-polyacrylamide gel analysis followed by autoradiography: two proteins were found in the normal cells that were not present in the transformed cells, and two proteins were found in the transformed cells that were not found in the normal cells. These results indicate that transformation of human fibroblasts is accompanied by only limited alteration in genetic expression. (25 Refs)

9. IMMUNOSELECTION OF SIMIAN VIRUS 40 LARGE T ANTIGEN MESSENGER RNAS FROM TRANSFORMED CELLS.

Oren M, Levine AJ

(c/o Levine) Dept. Microbiology, State Univ. New York Sch. Medicine, Stony Brook, NY, 11794

Virology; 113(2):790-793 1981

The messenger RNAs (m-RNAs) coding for the simian virus 40 (SV40) large tumor antigen were substantially purified by immunoprecipitation of polysome fractions from SV40-transformed cells. The level of SV40 T antigen m-RNA in the transformed cell used in this study was estimated at 0.05% of the total population of polyadenylated m-RNAs and a several-hundred-fold purification of this m-RNA was achieved by employing antibodies to SV40 large T antigen purified by either of two methods. The procedures described in this communication should be particularly useful for the immunoselection and purification of low-abundance m-RNAs or when the antigen is not available in large quantities. (Author abstract) (12 Refs)

10. INHIBITION OF ADENOVIRUS-TRANSFORMED CELL ONCOGENICITY BY ADENO-ASSOCIATED VIRUS.

Ostrove JM, Duckworth DH, Berns KI

Dept. Microbiology, Johns Hopkins Univ., Sch. Medicine, Baltimore, MD, 21205

Virology; 113(2):521-533 1981

Adeno-associated virus (AAV) has been shown to inhibit the oncogenicity and transforming ability of adenovirus (Ad). Using the H14b Ad-transformed hamster cell line, we have developed a model system in which to characterize the molecular events responsible for these inhibitory effects. AAV infection of H14b cells decreases their oncogenicity by approx threefold. The tumors that do arise are significantly smaller and have a longer latent period. AAV infection also alters the in vitro properties of the H14b cells, reducing cloning efficiency in methyl cellulose by 38-92% and saturation density by two- to four-fold. The molecular basis of this inhibition appears to be an inhibition of production of the 58K tumor antigen as determined by fluorescent antibody and immunoprecipitation studies. The reduction in the levels of tumor antigens are not due to alterations or loss of the Ad genome within H14b cells but may reflect an alteration in transcription or processing of Ad-specific mRNA. AAV infection of H14b cells does not lead to detectable levels of AAV DNA synthesis, but some AAV transcripts are made. This is the first instance in which AAV transcription has been detected in an Ad-transformed cell line. (Author abstract) (42 Refs)

11. BIOSYNTHESIS AND HORMONE-REGULATED EXPRESSION OF SECRETORY GLYCOPROTEINS IN RAT LIVER AND HEPATOMA CELLS. EFFECT OF GLUCOCORTICOIDS AND INFLAMMATION.

Baumann H, Held WA

Dept. Cell and Tumor Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263

J Biol Chem; 256(19):10145-10155 1981

Exposure of rat hepatoma tissue culture cells to dexamethasone results in appearance of a new glycoprotein, gp35-50 (Mr = 35,000 to 50,000) and increased synthesis of another glycoprotein, gp50 (Mr = 50,000). The glycoproteins synthesized in a fractionated cell-free translation system (containing dog pancreas microsomes) appear as a well separated series of spots on two-dimensional polyacrylamide gels which differ in size and charge. Glycoproteins synthesized by glucose-starved cells show similar size and charge heterogeneity. The size heterogeneity consists of a series of spots, each differing in mol wt by about 3,000, which could be almost completely abolished by treatment with endo-beta-N-acetylglucosaminidase H. Our results indicate that unglycosylated gp50 (Mr = 42,000) typically acquires three N-glycan units, whereas gp35-50 (Mr = 22,000) possesses eight N-glycosylation sites. Analysis of the cell-free translation products directed by mRNA from hepatoma tissue culture cells grown in tissue culture, from hepatoma tissue, and from normal liver tissue indicated that administration of dexamethasone causes a pronounced increase in gp35-50 mRNA in all three tissues. A similar increase was observed in liver after inflammation which along with other biochemical properties suggests that gp35-50 may be alpha1-acid protein. In contrast, mRNA coding for gp50 was not increased by dexamethasone in tumor tissue and no protein structurally related to gp50 was detected in the liver mRNA translation products. Thus, gp35-50 is expressed in normal liver, whereas gp50 is expressed in hepatoma cells and is differentially regulated by steroid hormones depending on whether the cells are grown in tissue culture or as a tumor in the rat. (Author abstract) (53 Refs)

12. ACCUMULATION OF NEWLY SYNTHESIZED MRNAS IN RESPONSE TO HUMAN FIBROBLAST (BETA) INTERFERON.

Colonno RJ

Central Res. and Development Dept., Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, DE, 19898

Proc Natl Acad Sci USA; 78(8):4763-4766 1981

Treatment of human fibroblast cells with human fibroblast (beta) interferon for up to 8 hr resulted in the accumulation of at least four mRNAs. The mRNAs were isolated from cellular polysomes and characterized by stimulation of translation in a wheat germ cell-free protein synthesis system. The mRNAs appear as early as 2 hr after exposure to interferon and can be translated in vitro into proteins having mol wt of 61,000, 62,000, 64,000, and 68,000. The response is not elicited by mouse interferon or insulin and does not occur in the presence of actinomycin D. Chase experiments indicated that the induced mRNAs remain ribosome-associated for at least 3 hr after their synthesis. The appearance of the induced mRNAs correlated directly with the onset of an antiviral state. Velocity sedimentation of the induced mRNAs on sucrose gradients demonstrated that each of the four induced proteins are encoded by different-sized mRNAs. (Author abstract) (23 Refs)

STRUCTURE AND LEVELS OF TRANSFER RNA

13. INHIBITION OF AMINOACYLATION OF TRANSFER RNA AND INDUCTION OF STRINGENT CONTROL IN ESCHERICHIA COLI BY 4-HYDROPEROXYCYCLOPHOSPHAMIDE.

Frank S, Eck W, Kersten W, Ogilvie A

Institut fur Physiologische Chemie, Universitat Erlangen-Nurnberg, Fahrstrasse 17, D-8520 Erlangen, W. Germany

Hoppe Seylers Z Physiol Chem; 362(8):1059-1068 1981

The compound 4-Hydroxycyclophosphamide, a highly cytotoxic derivative of cyclophosphamide, has bacteriostatic properties at concentrations higher than 80 uM when given to Escherichia coli growing in glucose/salt medium. The inhibitory effect on growth, protein and RNA syntheses is relieved by the addition of a mixture of amino acids, with leucine being obligatory. In cells treated with the drug, aminoacylation of tRNALeu is drastically decreased, but the content of free leucine is not. It is concluded that 4-hydroxycyclophosphamide interferes with the charging process of tRNALeu in E coli leading to an inhibition of protein synthesis. The concomitant inhibition of RNA synthesis can adequately be explained by the stringent response phenomena. In a relaxed mutant strain of E coli, protein synthesis is also inhibited, but the accumulation of RNA continues after the addition of the drug. Guanosine tetraphosphate, the putative mediator of the stringent control, accumulates in drug-treated stringently controlled E coli but not in the relaxed mutant. An additional direct effect of the drug on RNA synthesis can therefore be ruled out. (Author abstract) (27 Refs)

14. NUCLEOTIDE SEQUENCES OF TWO ASPARTIC ACID TRNAS FROM RAT LIVER AND RAT ASCITES HEPATOMA.

Kuchino Y, Shindo-Okada N, Ando N, Watanabe S, Nishimura S

Biology Div., Natl. Cancer Center Res. Inst., Chuo-ku, Tokyp 104, Japan

J Biol Chem; 256(17):9059-9062 1981

The nucleotide sequences of the major tRNAAsp from rat liver and a minor tRNAAsp present specifically in rat ascites hepatoma were determined by combined use of several postlabeling procedures. The sequence of rat liver tRNAAsp was determined to be pU-C-C-U-C-G-U-U-A-G-U-A-psi-A-G-U-G-G-D-G-A-G-U-A-U-C C-C-C-G-C-U-C-man Q-U-C-A-m5C-G-C-G-G-G A-G-A-m5C-m5C-G-G-G-G-T-psi-C-G-A U-U-C-C-C-G-A-C G-G-G-G-A-G-C-C-AOH. The nucleotide sequence of rat ascites hepatoma tRNAAsp was found to be the same as that of rat liver tRNAAsp, except that mannose-attached queuosine (manQ) present in the wobbling position of rat liver tRNAAsp was replaced by normal guanosine in rat ascites hepatoma tRNAAsp. The other modified nucleosides in the two tRNAAsp species were the same. Thus it was concluded that the new isoacceptor species of tRNAAsp that appears in the tumor tissue is due to hypomodification with respect to Q in the posttranscriptional process. The most notable feature on the sequence of the mammalian tRNAAsp is that cytidine is present in the position next to the 5'-end of the anticodon, because the only known tRNAs having cytidine in this position are cytoplasmic initiator tRNAs from multicellular eukaryotic organisms. (Author abstract) (21 Refs)

15. BIOLOGICAL AND STRUCTURAL DIFFERENCES BETWEEN TRNAVAL SPECIES ISOLATED FROM RAT ASCITES HEPATOMA CELLS AND NORMAL RAT LIVER.

Shindo-Okada N, Kuchino Y, Harada F, Okada N, Nishimura S
Biology Div., Natl. Cancer Center Res. Inst., Tsukiji, Chuo-ku, Tokyo 104, Japan
J Biochem (Tokyo); 90(2):535-544 1981

On RPC-5 column chromatography, the main valine acceptor activity of tRNA (tRNA2Val) from rat ascites hepatoma cells was eluted later than that of normal rat liver tRNA (tRNA1Val). The tRNA2Val was aminoacylated by E coli amino-acyl-tRNA synthetase, while tRNA1Val from normal rat liver was not. Rat fetal liver tRNAVal was also aminoacylated by E coli aminoacyl-tRNA synthetase. tRNA1Val (rat liver) and tRNA2Val (ascites hepatoma) were each purified to a homogeneous state by RPC-5 column chromatography and two-dimensional polyacrylamide gel electrophoresis, and their sequences were determined by post-labeling techniques. Ascites hepatoma tRNA2Val differed from rat liver tRNA1Val in that Gm18, C32 and an unknown modified nucleoside, N34, in the latter tRNA were mostly replaced by G, Cm, and inosine, respectively. In addition, 3'-terminal adenosine was not present in tRNA1Val (normal rat liver), but was in tRNA2Val (ascites hepatoma). Other modifications and the primary structures of the two tRNAVals were found to be the same. Thus it was concluded that the new isoacceptor species of tRNAVal in ascites hepatoma cells is due to a change of post-transcriptional modification, not to a change of tRNA transcription. The unique feature of the change post-transcriptional modification in tRNA2Val (ascites hepatoma) is that both hypo- and hypermodification take place simultaneously in the tRNA molecule depending the locations of nucleotide residues. (Author abstract) (33 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

16. IN VITRO SYNTHESIS AND MODIFICATION OF MRNA BY EXVECTORIAL ISOLATES OF WOUND TUMOR VIRUS.

Nuss DL, Peterson AJ
Div. Lab. and Res., New York State Dept. Health, Albany, NY, 12201
J Virol; 39(3):954-957 1981

Nontransmissible (exvectorial) isolates of wound tumor virus retain the ability to catalyze in vitro synthesis of RNA. Furthermore, exvectorial virus particles exhibit mRNA-2'-O-methyltransferase activity even after long-term (30-yr) passage in a host that lacks this enzyme activity. (Author abstract) (22 Refs)

OTHER RELATED STUDIES

17. ANALYSIS OF ENDOGENOUS AVIAN RETROVIRUS DNA AND RNA: VIRAL AND CELLULAR DETERMINANTS OF RETROVIRUS GENE EXPRESSION.

Baker B, Robinson H, Varmus HE, Bishop JM
(c/o Bishop) Dept. Microbiology and Immunology, Univ. California, San Francisco, San Francisco, CA, 94143
Virology; 114(1):8-22 1981

We have characterized endogenous avian retrovirus DNAs and RNAs in uninfected white leghorn chicken embryos. The embryos we studied include representations of four phenotypic classifications of chickens (gs- chf-, gs+ chf+, gs- chf+, and V+), and contained the endogenous proviruses evl, 2, 3, 4, 5, 6, 8, 9, and 15. We confirmed the previously described phenotypes and restriction maps of evl, 3, 4, 5, 6, 8, and 15, and we confirmed the phenotype for ev9 and derived a restriction map for this locus. Evaluation of the structure of the individual proviruses and characterization of the nuclear and cytoplasmic viral RNA isolated from embryos of defined genotype yielded the following major conclusions. (i) Viral RNA could not be detected for ev4, ev5, ev8, or ev15. (ii) The amount of stable RNA produced from evl, ev3, ev6, or ev9 varied over a range of at least 100-to 300-fold and was at least 10-to 1,000-fold lower than the amounts found in cells productively infected with exogenous avian retroviruses. (iii) A deletion in the provirus at ev3 can account for three abnormalities: the production of a viral protein that results from fusion of internal regions of the gag and pol genes, the abnormal structure of a subgenomic viral RNA, and failure of the abnormal RNA to appear in the cytoplasm. (iv) A deletion in the provirus at ev6 gives rise to at least two major anomalies: the initiation of transcription at an upstream cellular promoter, and the abnormal metabolism of an ev6 viral RNA. (v) ev9 has an ostensibly normal structure; nevertheless, the metabolism of an RNA arising from this locus is aberrant. We conclude that the expression of endogenous retrovirus genes in chickens is subject to control by both viral and cellular determinants. (Author abstract) (59 Refs)

18. ONCOGENICITY OF GIBBON RETROVIRUS DETERMINED BY LEUKEMIA-SPECIFIC GENOMIC SEQUENCES.

Sun L, Kawakami TG
(c/o Kawakami) Comparative Oncology Lab., Univ. California, Davis, CA, 95616
Virology; 114(1):261-264 1981

The genome of a Type C virus, GaLV-5, isolated from several clinically healthy gibbons, was examined for the presence of nucleotide sequences related to the myelogenous leukemia-specific 'MYE' RNA and the lymphocytic leukemia-specific 'LYM' RNA which have been isolated from several strains of oncogenic GaLV. The genomes of these oncogenic GaLVs were each separated into sequences homologous and nonhomologous to GaLV-5. Based on hybridization analysis, the nonhomologous RNA fractions were found to contain either the MYE RNA or the LYM RNA. This indicates that the leukemia-specific RNAs are lacking in the genome of GaLV-5. This lack was further confirmed by analysis of hybridization kinetics. The presence of leukemia-specific RNA sequences in GaLV genomes that were isolated from animals with leukemia and the absence of these sequences in virus strains isolated from animals free of clinical symptoms of leukemia indicate that the leukemia-specific RNA sequences are closely associated with the oncogenesis of leukemia in gibbons. (Author abstract) (17 Refs)

19. STUDIES ON THE INDICATORS FOR THE RESPONSIVENESS OF HUMAN BREAST CANCER TO SEX STEROIDS.

Boku S
Dept. Obstetrics and Gynecology, Kyoto Prefectural Univ. Medicine, Kyoto 602, Japan
Nippon Naibunpi Gakkai Zasshi; 57(1):64-88 1981

Characteristics of steroid receptors in breast cancer were investigated to determine indicators of response to treatment for breast cancer. First, steroid receptors in breast cancer tissues were characterized by means of dissociation constants in tissues from premenopausal and postmenopausal patients; dissociation constants were determined with the aid of charcoal absorption at 4 C for estradiol-17beta-estrogen receptors (ERs), R5020-progesterone (PR) receptors, 5alpha-dihydrotestosterone (DHT)-androgen receptors (ARs), and R1881-ARs. These receptors sedimented to 7-6S and 5-4S regions; the 7-6S binding was easily dissociated with 5-20% sucrose gradient centrifugation. ARs and PRs were contained in the R1881-cytosol bindings. Cytosolic steroid receptor levels were analyzed in each case, and max binding sites were analyzed by Scatchard plot analysis. Nuclear receptors were determined by exchange assay; nuclear PRs and ARs were detected in a few cases, and nuclear ERs were detected while cytosolic ERs were not detected. Results of studies of nuclear binding of steroid receptor complexes substituting ERs and PRs of rabbit uterine cytosol for the human breast cancer tissues suggested that part or all of the nuclear receptor-binding sites of breast cancer tissues are defective in some tumor nuclei. The existence of receptors in the cytosol or nuclei, nuclear binding of receptor-steroid complexes, or measurement of nuclear RNA synthesis by steroid receptors in breast cancer cells were thought to be effective indicators of the endocrine-therapy response of breast cancer. (34 Refs) (In JPN)

20. ISOLATION AND CHARACTERIZATION OF POLYPLOID NUCLEI OF R3230AC MAMMARY ADENOCARCINOMA AND COMPARISON WITH NORMAL MAMMARY NUCLEI.

Kulick D, Liu DK
(c/o Liu) Dept. Pharmacology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Cancer Res; 41(10):3907-3912 1981

The R3230AC mammary adenocarcinoma is biochemically similar to the normal lactating mammary gland in many ways, including the RNA/DNA ratio. However, the tumor differs from normal in important ways, which include having a DNA content 2 to 4x higher than the max value for normal mammary gland. This raises the question of whether the cells of the tumor all have more DNA than normal cells. In order to determine how tumor DNA is distributed and whether its transcriptional activity differs from normal, we have compared the ploidy and RNA polymerase activities of nuclei isolated from both sources. Nuclei were also examined for their content of Ca++-stimulated RNase activity, a marker of mammary differentiation. Sucrose density gradient centrifugation of tumor cell nuclei revealed three nuclear types, designated T1, T2, and T3, representing 25, 48, and 27% of total nuclei isolated. T1, T2, and T3 nuclei contained, respectively, 6.5, 12.3, and 19.0 pg DNA per nucleus, representing diploid, tetraploid, and hexaploid amounts of DNA. Nuclear RNA and protein increased in proportion to ploidy. By contrast, cell nuclei isolated from lactating mammary gland formed only two bands (M1 and M2), comprising 54 and 46%, respectively, of total nuclei isolated. Both M1 and M2 nuclei contained diploid amounts of DNA. Therefore, the higher DNA content in the tumor is attributable, at least in part, to the presence of polyploid nuclei in the majority of tumor cells. The combined activity of DNA-dependent RNA polymerases I, II, and III per nucleus was the same in T1, T2, and T3; M1 and M2 also had activities similar to each other but much lower than the tumor types. Activity attributable to polymerase I (resistant to 200 ug alpha-amanitin per ml), polymerase II (inhibited by 0.06 ug alpha-amanitin per ml), and polymerase III (inhibited by 200 ug alpha-amanitin per ml) was about 35, 50, and 15%, respectively, for each class of tumor nuclei. The corresponding values for M bands were about 44, 34, and 22%. These results suggest that tumor cells synthesize more heterogeneous RNA than do mammary cells of lactating rats, but the latter synthesize more ribosomal RNA. Activity of mammary-specific Ca++-stimulated RNase increased slightly per nucleus as the ploidy of tumor nuclei increased, but in every T group the activity was less than one-half of that of M1 or M2 nuclei. Thus, despite differences in ploidy, all tumor nuclear classes show a lesser degree of differentiation than nuclei from the lactating gland, with respect to their capacity for synthesis of ribosomal RNA compared to messenger RNA and their expression of Ca++-stimulated RNase. (Author abstract) (31 Refs)

21. INTERACTION OF PSORALEN DERIVATIVES WITH THE RNA GENOME OF ROUS SARCOMA VIRUS.

Swanstrom R, Hallick LM, Jackson J, Hearst JE, Bishop JM
Dept. Microbiology and Immunology, Univ. California, San Francisco, CA, 94143
Virology; 113(2):613-622 1981

We have examined the interaction of several psoralen derivatives with the RNA genome of Rous sarcoma virus (RSV). In the presence of long-wavelength UV light, 4,5'8,-trimethylpsoralen (trioxsalen) and its 4'-hydroxymethyl (HMT) and 4'-aminomethyl (AMT) derivatives all efficiently crosslinked the subunits of the RSV 70 S RNA complex into a nondissociable state. These psoralen derivatives also were able to penetrate virions and crosslink the RNA complex in situ. The ability of psoralen to crosslink the subunits of viral RNA in situ is consistent with the presumption that the RSV genome exists as a complex within the virion and suggests an approach for a detailed examination of regions of secondary structure. The addition of psoralen adducts to viral RNA correlated with a loss of virus infectivity and a decrease in the amount and length of viral DNA synthesized in vitro and in vivo. Our results indicate that the RSV genome contains a significant amount of secondary structure that is reactive with psoralen compounds and that the addition of HMT to viral RNA causes premature chain termination during viral DNA synthesis. (Author abstract) (42 Refs)

22. INTERFERONS, DOUBLE-STRANDED RNA, AND RNA DEGRADATION. ISOLATION AND CHARACTERIZATION OF HOMOGENEOUS HUMAN (2'-5')(A)N SYNTHETASE.

Yang K, Samanta H, Dougherty J, Jayaram B, Broeze R, Lengyel P

Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, CT, 06511

J Biol Chem; 256(17):9324-9328 1981

One of the mediators of interferon action is (2'-5')(A)n synthetase. If activate d by double-stranded RNA it converts ATP into pyrophosphate and (2'-5')(A)n. In turn, (2'-5')(A)n activates a latent endoribonuclease (RNase L) which cleaves single-stranded RNA. We report here the isolation and characterization of a homogeneous human (2'-5')(A)n synthetase. The enzyme was purified from interferon-treated HeLa S3 cells by chromatography of a ribosomal salt wash fraction on DEAE-cellulose, poly(I).poly(C) agarose, and CM-cellulose. The purified (2'-5')(A)n synthetase can convert over 90% of ATP into (2'-5')(A)n. The enzyme is unstable but can be stabilized by certain nonionic detergents (eg Triton X-100). Its apparent Mr = 100,000, as determined by gel electrophoresis in sodium dodecyl sulfate, and about 80,000, as determined by centrifugation through a glycerol gradient. The human (2'-5')(A)n synthetase is similar to the corresponding enzyme from mouse Ehrlich ascites tumor cells, but differs from the latter size (100,000 vs 105,000 daltons) and in ionic conditions required for max activity. (Author abstract) (33 Refs)

23. STRIKING SIMILARITIES ARE EXHIBITED BY TWO SMALL EPSTEIN-BARR VIRUS-ENCODED RIBONUCLEIC ACIDS AND THE ADENOVIRUS-ASSOCIATED RIBONUCLEIC ACIDS VAI AND VAII.

Rosa MD, Gottlieb E, Lerner MR, Steitz JA

Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, CT, 06510

Mol Cell Biol; 1(9):785-796 1981

The nucleotide sequence of the Epstein-Barr virus genome region coding two small RNAs (EBER 1 and EBER 2) was determined. Both EBERs are coded with a 707-base pair HaeIII/HaeIII fragment near the right-hand end of the EcoRI J/SstI fragment. The 5' terminal oligonucleotide for both is pppAGGAC. Both EBERS show heterogeneity at the 3' end. EBER 1 is 166 (167) nucleotides long. EBER 2 is 172+-1 nucleotides long. Both EBERs are transcribed from the same DNA strand; they are separated by 161 base pairs. The two EBERs show considerable homology, with the greatest in the areas of the 5' termini, around nucleotides 20 and 65, and near the 3' termini. Genes for both EBERs were transcribed by RNA polymerase III. Marked similarities exist between EBERs 1 and 2 and adenovirus-associated RNAs VAI and VAII. All are 160-170 nucleotides long and are transcribed in the same direction on their respective genome strands. Intragenic control regions for the four RNAs are homologous. All four RNAs form nucleoprotein complexes that precipitate with anti-La antibodies associated with systemic lupus erythematosus. Protein from uninfected HeLa cells conferred antigenicity on each of the four RNAs, indicating that antigenicity is conferred by host-cell rather than viral protein. (31 Refs)

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RNA TRANSCRIPTION/ SYNTHESIS

1. TRANSCRIPTION OF T-DNA IN OCTOPINE AND NOPALINE CROWN GALL TUMOURS IS INHIBITED BY LOW CONCENTRATIONS OF ALPHA-AMANITIN.

Willmitzer L, Schmalenbach W, Schell J
Abteilung Schell, Max-Planck-Institut fur Zuchtungsforschung, D-5000 Koln 30, W. Germany
Nucleic Acids Res; 9(19):4801-4812 1981

Highly purified and physiologically active nuclei were isolated from four different octopine and nopaline crown gall lines. These nuclei exhibited a high endogenous RNA synthesizing activity involving all three RNA-polymerases I, II and III. Isolated nuclei were shown by Southern blotting to synthesize T-

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DNA specific RNA. This system was shown to be sensitive to actinomycin-D and therefore to be DNA-dependent. The transcription of the T-DNA was also inhibited for more than 90% by low concentrations of alpha-amanitin (0.7 ug/ml) indicating that the T-DNA, although from bacterial origin, is transcribed by the host RNA polymerase II. (Author abstract) (35 Refs)

2. EFFECT OF ACTIVATORS OF CAMP ACCUMULATION ON VARIOUS STAGES OF GENOME EXPRESSION DURING ACUTE RADIATION INJURY. COMMUNICATION I. EFFECT OF SEROTONIN AND PAPAVERINE ON BIOSYNTHESIS AND RELEASE OF RNA FROM NUCLEI OF LIVER AND SPLEEN CELLS IN EARLY PERIOD AFTER WHOLE-BODY X-IRRADIATION OF RATS.

Tsudzevich BA, Galkina LA, Kucherenko NE
Faculty Biology, T. G. Shevchenko State Univ., Kiev, USSR
Radiobiologiia; 21(4):495-502 1981

The effect of serotonin (ST) and papaverine (PV) on RNA biosynthesis and release from the nuclei of liver and spleen cells was studied in albino rats subjected to whole-body irradiation with 800 R. Administration of ST alone or in combination with PV prior to irradiation stimulated accumulation of cyclic AMP and stabilized RNA synthesis both in radioresistant liver and in radiosensitive spleen. (12 Refs) (In RUS)

STUDIES OF HETEROGENEOUS NUCLEAR RNA

3. DIFFERENT FREQUENCY CLASSES OF SEQUENCES IN HETEROGENEOUS NUCLEAR RNA OF NORMAL PROMYELOCYTES AND LYMPHOBLASTS OF LEUKEMIC BLAST CELLS OF CIRCULATING BLOOD AND THE HL60 LINE.

Torelli U, Torelli G, Narni F, Donelli A, Ferrari S, Franchini G, Calabretta B
Istituto di Patologia Speciale Medica e Metodologia Clinica, Via del Pozzo, 71, 41100 Modena, Italy
Haematol Blood Transfus; 26:517-519 1981

The relative representation of sequence classes in heterogeneous nuclear (hn) RNA was determined in two types of normal cells (lymphoblasts and promyelocytes), three types of acute leukemia cells from untreated patients (acute lymphocytic and acute myelocytic leukemia blast cells from circulating blood), and HL60 promyelocytic cells. RNA was labeled by incubating cells with 3H-uridine. After sedimentation in a preparative sucrose gradient, fractions with S values greater than 50 were pooled and used in the hybridization reaction with normal DNA. The reaction was carried out in 70% formamide and the DNA/RNA ratio was at least 5 x 10(3). Hybridization experiments indicated the presence in hnRNA of normal cells of three kinetic classes of sequences, while in hnRNA of leukemic cells there were only two second order components, roughly corresponding to the first and second class of sequences revealed in hnRNA of the normal cells. The least squares computer analysis applied to the hybridization values showed that hnRNA of normal hemopoietic cells includes a class of sequences with very low abundance which is absent in leukemic cells. (7 Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

4. A STUDY ON THE ACTIVITIES OF INTERFERON MESSENGER RNA.

Yang C, Hou Y, Yang X, Fu Q, Liu L, Wu S, Li Y
Inst. Virology, Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Weishengwuxue He Mianyixue Zazh; 1(1):11-17 1981

Translation activities of interferon messager RNA are described, using oocytes of Tilapiamosiabica peters (TP) and those of Xenopus laevis as translation systems. The interferon messenger RNA (mRNA) used as derived from murine cell lines, including LpA, L929 B and Ehrlich ascitic carcinoma (LEA) cells. Newcastle disease virus was used as the interferon inducer. Results showed that translation efficiencies were similar in both systems. The highest translation efficiency was obtained when TP oocytes treated with nRNA were cultured in Eagle's medium containing 0.01% HEPES and 0.5% NaHCO3 at pH 7.5 and 25 C; other culture media such as Hultfreters' medium and saline yielded considerably lower translation efficiencies. The nucleotide ppp A'2p5'A'2p5'A (or 2'-5'P3A3) at 500 nM concentration did not affect translation efficiency (17.4%) compared to 16.9% of control, but at 1 uM it caused a slight inhibition (14.9%). The concentrations of interferon mRNA in virus-induced LpA cells were directly related to the antiviral activities of translation products in the TP oocytes, suggesting that the amount of interferon mRNA can be determined by the interferon activities of its translation products. (16 Refs) (In CHI)

5. FURTHER HETEROGENEITY OF HUMAN ALPHA INTERFERON MRNA SPECIES.

Sehgal PB, Sagar AD, Braude IA
Rockefeller Univ., New York, NY, 10021
Science; 214(4522):803-805 1981

Translationally active (in Xenopus oocytes) human alpha interferon (IFN) messenger RNA's (mRNA's) derived from Sendai virus-induced WBC cultures display a bimodal distribution of RNA lengths on electrophoresis through agarose-CH3HgOH gels. The major population (alphas) consists of mRNA of length 0.7 to 1.4 kilobases, while the minor population (alphaL) consists of RNA of length 1.6 to 3.5 kilobases. Induction of human WBC in the presence of 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole (DRB; 100 micromolar) appears to inhibit the accumulation of IFN-alphas and to enhance that of IFN-alphaL mRNA's (av length about 1.8 kilobases in preparations from DRB-treated cells). Interferons derived from the alphas mRNA's represent the group of previously recognized alpha interferons while the alphaL interferons are distinguishable from this group by their lower heterospecific activity on bovine cells compared to human cells, their apparent slower mobility in sodium dodecyl sulfate-polyacrylamide gels, and their apparent heteroclitic response toward an antiserum to IFN-alpha. (Author abstract) (15 Refs)

6. INTERFERON-INDUCED ENZYMES: FUNCTION, ASSAY AND APPLICATION (MEETING ABSTRACT).

Revel M, Wolf D, Shulman L, Merlin G, Schattner A, Wallach D, Kimchi A

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Thirteenth Miami Winter Symposium: Cellular Responses to Molecular Modulators, January 12-16, 1981, Miami, Florida. University of Miami 112 pp., 1981.

A prominent biochemical activity of all interferons (IFN) is the induction in sensitive cells, of several translation regulatory enzymes. We have developed an assay for the messenger (m) RNA of one of these enzymes, the (2'-5') oligo A synthetase. Escherichia (E) Xenopus oocytes are injected with poly A+ RNA from cells treated with interferon, and the oocyte extract adsorbed to poly (rI): (rC)-agarose beads is incubated with ATPE. In this way the formation of (2'-5') (Ap) nA cores and of translation inhibitory activity can be demonstrated. The assay was applied to mouse L cell cultures and to human HeLa, SV80 and Namalva cells. In all cases there was no E-mRNA acitivity in the cytoplasm of cells not treated by interferon. The mRNA activity started to appear at 3 hr post-infection and increased 10-fold from 3 to 8 hr after interferon. The E-mRNA from human cells sedimented as a sharp peak at 16S on sucrose gradients. The (2'-5') oligo A synthetase purified several thousand fold from human cells behaves as a 30,000 Mr enzyme on Sephacryl 200 columns. In some cells, the level of (2'-5') oligo A synthetase is high even in the absence of exogenous interferon treatment. Using a simpler assay for the (2'-5') oligo A synthetase in cells obtained from 1 ml of blood we have observed that in peripheral human blood mononuclear cells, the level of enzyme is high but very constant (+/-35%). In 30% of lymphatic leukemias the enzyme levels were lowered (to 10-40% of the normal value). These functions of interferon-induced (2'-5') oligo A synthetase will be discussed in relation to the anti-mitogenic effect of synthetic (2'-5') oligo A cores on mitogen-stimulated lymphocytes and fibroblasts, and the growth-related variations in the level of the enzyme that synthesize and degrade this oligonucleotide. (no Refs)

7. SYNTHESIS AND PROCESSING OF THE ALPHA HEAVY CHAINS OF SECRETED AND MEMBRANE-BOUND IGA.

Kikutani H, Sitia R, Good RA, Stavnezer J

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Proc Natl Acad Sci USA; 78(10):6436-6440 1981

We have compared the synthesis and processing of Ig alpha chains in two murine cell lines, a B cell lymphoma that expresses membrane-bound IgA and a hybridoma that secretes IgA. Results of biosynthetic labeling experiments demonstrated that membrane-bound and secreted alpha chains have two distinct intracellular precursors, of different mol wt and isoelectric points. RNAs from both of these cell lines direct the synthesis in vitro of two alpha polypeptides of Mr 59,000 and 62,000, the larger one being the precursor for membrane-bound alpha chain and the smaller one being the precursor for secreted alpha chain. These cell lines each contain three RNAs, 1.7, 2.1, and 3.1 kilobases in length, which hybridize with cDNA for the alpha constant region and which are present in different concentrations. Our results suggest that the smallest RNA encodes the secreted alpha chain and one or both of the larger RNAs encode(s) the membrane-bound alpha chain. (Author abstract) (33 Refs)

8. MECHANISMS OF KIRSTEN MURINE SARCOMA VIRUS TRANSFORMATION-INDUCED CHANGES IN THE COLLAGEN PHENOTYPE AND SYNTHETIC RATE OF BALB 3T3 CELLS.

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Proc Natl Acad Sci USA; 78(10):6028-6032 1981

Specific viral transformation rather than cell selection can explain the previously observed increase in the proportion of Type III procollagen compared to Type I procollagen in BALB 3T3 cells transformed by Kirsten murine sarcoma virus (Ki-MSV). Two subclones of BALB 3T3 A31 were productively infected with a temperature-sensitive Ki-MSV in the presence of helper murine leukemia virus (MLV), resulting in virtually complete transformation of cultures and eliminating selection of transformed foci. Analysis of radioactive collagen, derived from procollagen by pepsin treatment, showed that both of the tsKi-MSV/MLV-transformed subclones contained a four-fold greater proportion of Type III procollagen than did control MLV-infected cultures. A nonproducer derivative exhibited an even greater change (10-fold), indicating that viral replication was irrelevant. After 48 hr at a nonpermissive temperature, tsKi-MSV-transformed cells retained a high proportion of Type III procollagen, suggesting that either this change is not induced by src protein or else there is a slowly reversible or irreversible step involved. Alternatively, Type III procollagen mRNA may be long lived. In contrast, the relative rate of procollagen synthesis in transformed cells was clearly regulated by src protein. Translation of mRNA from cells preincubated at permissive or nonpermissive temperatures revealed that the decreased relative rate can be explained by a simultaneous small decrease in the level of procollagen mRNA and a large increase in mRNA for noncollagen proteins. (Author abstract) (36 Refs)

9. CELLULAR HOMOLOGUE (C-SRC) OF THE TRANSFORMING GENE OF ROUS SARCOMA VIRUS: ISOLATION, MAPPING, AND TRANSCRIPTIONAL ANALYSIS OF C-SRC AND FLANKING REGIONS.

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Proc Natl Acad Sci USA; 78(9,part2):5842-5846 1981

The tumorigenic properties of Rous sarcoma virus are attributable to a 60,000-dalton protein, pp60v-src, encoded by a single viral gene, v-src, A homologous gene, c-src, that contains the information for a 60,000-dalton protein, pp60c-src, has been identified in all tested vertebrate cells. By screening a recombinant DNA library representative of the chicken genome, we isolated two overlapping DNA fragments that contain more than 30 kilobases (kb) of DNA spanning the coding sequences for pp60c-src. This 30-kb region is devoid of moderately or highly repeated sequences and shares homology with the entire viral gene and noncoding sequences 5' of v-src. Although v-src has an uninterrupted coding sequence, c-src is interrupted by a minimum of seven intervening sequences. At least two polyadenylylated RNAs seem to be encoded within the DNA we have isolated. The larger RNA, approx 3.9 kb, is the presumptive c-src mRNA; the smaller transcript of about 2 kb hybridizes to DNA sequences several kb from the 3' end of the v-src/c-src homology area. (Author abstract) (28 Refs)

10. SEQUENCE DIVERGENCE OF NUCLEUS-CONFINED POLYADENYLATED RIBONUCLEIC ACIDS IN FRIEND ERYTHROLEUKEMIC CELLS.

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Wolfson Lab. Molecular Pathology, Beatson Inst. Cancer Res., Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1BD, Scotland
Biochemistry; 20(21):6257-6264 1981

For determination of whether any potential protein-coding RNA sequences are confined to the nucleus in Friend cells, a comparison has been made of the sequence divergence of polyadenylated RNA molecules which are either nucleus confined or transported to the cytoplasm. Both unique DNA and cDNA probes enriched in such sequences were reacted with a large excess of mouse or rat DNA. The extent of hybridization and the thermal stability of hybrids formed under various stringency conditions were used as a measure of the amount of sequence divergence which had taken place. The results confirmed that messenger sequences are relatively conserved during evolution. Furthermore, experiments involving both unique DNA probes representative of the full length of nucleus-confined RNA molecules and cDNA probes complementary to their poly(A)-adjacent fragments indicated that the polyadenylated nucleus-confined sequences have, on av, diverged during evolution much more than mRNA sequences. The vast majority of these sequences therefore probably do not represent potential mRNAs which are confined to the nucleus and subject to posttranscriptional control in a manner similar to those which have been demonstrated in sea urchins. (Author abstract) (40 Refs)

11. PLASMACYTOMAS WITH MORE THAN ONE IMMUNOGLOBULIN 5K 1 MRNA: IMPLICATIONS FOR ALLELIC EXCLUSION.

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Proc Natl Acad Sci USA; 78(9,part2):5812-5816 1981

Although only one allele of an Ig gene is thought to be expressed as a polypeptide by a given lymphocyte ('allelic exclusion'), three murine plasmacytomas were found to contain more than one kappa light chain mRNA species, as evidenced by the sequences of distinct kappa cDNA clones. Two different kappa cDNA sequences were cloned from BFPC 61 microsomal mRNA, two from MOPC 173, and three from S107. One cDNA sequence from each tumor matches the known secreted polypeptide, while the variant sequences differ in the variable (V) region. Hence fusion of a Vkappa gene to a joining (Jkappa) gene has occurred independently on separate homologous chromosomes and each allele is transcriptionaly competent. The BFPC 61 variant sequence contained a normal Vkappa sequence linked out of phase to Jkappa2; hence allelic exclusion in this line is accounted for by an error in DNA rearrangement. One S107 variant cDNA has an untranslatable sequence linked to Jkappa-Ckappa and may derive from a non-Vkappa or pseudo-Vkappa gene fused to Jkappa. Another S107 variant cDNA, however, has a proper Vkappa linked in phase to Jkappa (albeit missing the first two germ-line Jkappa codons) and the MOPC 173 variant sequence also contains a proper Vkappa linked in phase to Jkappa (albeit missing the first 2 germ-line Jkappa codons) and the MOPC 173 variant sequence also contains a proper Vkappa-Jkappa join, although it does not encode a tryptophan residue common to all Ig chains. The presence of two potentially expressible kappa mRNAs in both S107 and MOPC 173 suggests that allelic exclusion does not hold in all lymphocytes, or that it sometimes reflects events subsequent to mRNA production, such as inability of certain kappa chains to assemble properly with the heavy chain. These observations are compatible with a stochastic model for allelic exclusion in which productive and nonproductive V-J recombination events occur at a certain frequency for each allele. (Author abstract) (44 Refs)

12. CONTROL OF EXPRESSION OF HISTOCOMPATIBILITY ANTIGENS (H-2) AND BETA2-MICROGLOBULIN IN F9 TERATOCARCINOMA STEM CELLS.

Croce CM, Linnenbach A, Huebner K, Parnes JR, Margulies DH, Appella E, Seidman JG
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Proc Natl Acad Sci USA; 78(9,part2):5754-5758 1981

Murine teratocarcinoma stem cells, unlike most other cell types, do not express major histocompatibility antigens. The steady-state levels of beta2-microglobulin and H-2 mRNA from F9-derived teratocarcinoma stem and differentiated cells were examined by blot hybridization using cloned DNA probes specific for these mRNAs. No H-2-or beta2-microglobulin-specific RNA was detected in F9 teratocarcinoma stem cells (clone 12-1); thus, F9 teratocarcinoma stem cells (clone 12-1) contain no more than 1/10 the H-2 and beta2-microglobulin mRNAs of the differentiated daughter cells (clone 12-1a). We suggest that this regulation of major histocompatibility antigen expression is due to transcriptional control of the major histocompatibility antigen genes, H-2 and beta2-microglobulin. The transcriptional regulation of these genes is accompanied by a change in their DNase I sensitivity. Normally, transcriptionally inactive genes are DNase I resistant, while active genes are DNase I sensitive. In contrast, the silent major histocompatibility antigen genes of teratocarcinoma stem cells are more DNase I sensitive than the active genes of the differentiated cells. (Author abstract) (41 Refs)

13. SEQUENTIAL TRANSCRIPTION-TRANSLATION OF SIMIAN VIRUS 40 BY USING MAMMALIAN CELL EXTRACTS.

Cepko CL, Hansen U, Handa H, Sharp PA
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Mol Cell Biol; 1(10):919-931 1981

The expression of Simian virus 40 (SV40) was studied using the current technologies of recombinant DNA and in vitro transcription systems. The in vitro transcription of specific SV40 RNAs is described. A polypeptide comigrating with the 94K T antigen of SV40 was not present in products transcribed from Eco-RI-, PstI-, or TaqI-cleaved DNA. However, if a small fraction of the RNA transcribed from the Eco-RI-cleaved DNA had been processed by excision of the intervening sequences between 0.60 an 0.53 monitor units, synthesis of T (94K) would have been possible. Synthesis of the large T family of polypeptides is described. When the relative efficiencies of in vivo- and in vitro-synthetized RNA were quantitated, it was determined that in vitro small tumor antigen t messenger RNA (mRNA) is more efficiently translated than in vivo t mRNA. The translatability of the in vitro transcripts from the SV40 late regions was examined; the synthesis of the viral capsids VP1, VP2, and VP3 from RNA transcribed in vitro was studied. By using DNA templates cleaved within the late region, information concerning the identity of the transcripts that served as VP1, VP2, and VP3 messages was obtained.

RNAs synthesized in vitro were fractionated by size to allow the direct identification of VP1, VP2, VP3, and t mRNAs. Other topics discussed include the efficiency of in vitro RNAs as messages, assay for RNA splicing, initiation at internal AUG codons, synthesis of polypeptides by minor transcripts (assay for proteins specified by complementary DNA clones), and lack of termination in the inhibition of translation. (32 Refs)

14. VIRAL GENE EXPRESSION IN POLYOMA VIRUS-TRANSFORMED RAT CELLS AND THEIR CURED REVERTANTS.

Fenton RG, Basilico C
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J Virol; 40(1):150-163 1981

We have studied transcription of integrated viral DNA sequences in a variety of ts-a polyoma virus-transformed rat cells and cured revertants (which had undergone excision o f variable amounts of integrated viral DNA) to characterize the structure of viral mRNA's produced in these lines under conditions in which integrated DNA is stable. Our results indicate that cells containing intact early region sequences, either in single-copy or tandem insertions, produce mRNA's indistinguishable from those observed early in lytic infection; sequences complementary to the polyoma late region were not transcribed from integrated viral DNA. Cured revertants no longer encoded full-length early mRNA's, but produced viral transcripts whose 3' ends mapped at an alternative early region polyadenylic acid attachment site at 99 map units or extended into flanking host sequences. The phenotype of these revertant cells correlated with the abundance of these transcripts, suggesting that the transforming function(s) of polyoma virus controls the cellular phenotype in a dose-dependent manner. Unexpected results were obtained from studies of cells containing tandem repeats of defective viral DNA in which the polyadenylic acid attachment signal at 25.8 map units and surrounding sequences were deleted. In these cases, polyadenylated mRNA's were observed that contained sequences complementary to the early strand of the polyoma late region. These mRNA's (some larger than 8 kilobases) originated at the viral early promoter, extended into the late region, and continued into the early region of the contiguous repeat in the tandem. The multimeric mRNA's produced contained defective early regions in tandem with late region sequences. S1 analysis indicated that whereas the 5' early region sequences of readthrough transcripts were spliced in the usual manner, internal early region repeats were either unspliced or used only one of the small early region splices. When deletions in the viral DNA began 40 base pairs past the AAUAAA sequence at 25.8 map units, no readthrough transcripts were observed. This suggests that sequences nearby the AAUAAA sequence at 26 map units may control transcription termination of the polyoma early region. (Author abstract) (34 Refs)

15. IN VITRO TRANSLATION OF AVIAN MYELOBLASTOSIS VIRUS RNA.

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J Virol; 40(1):107-117 1981

Avian myeloblastosis virus (AMV)-infected cells contain two viral mRNA's, a genome-sized 34S (7.5-kilobase) mRNA and a 21S (2.5-kilobase) subgenomic mRNA, which contains the AMV-specific sequences (myb sequences). We found that AMV virions packaged both the 7.5-kilobase full-length genomic RNA and the 2.5-kilobase subgenomic RNA. In vitro translation of AMV virion RNA sized by sucrose density gradient centrifugation yielded 76,000-, 56,000-, 48,500-, 47,000-, and 32,000-dalton products. The 76,000-dalton protein was coded for by RNA throughout the gradient, but the peak of activity was at 34S to 35S. The 56,000- , 48,500-, and 32,000-dalton proteins were encoded in a 21S RNA, and the 47,000-dalton protein was encoded in an RNA of approx 24S. The 76,000-dalton protein was identified as Pr76gag, based upon immunoprecipitation with specific antiserum and the presence of the 19* dipeptide. 7-Methylguanosine triphosphate inhibited the syntheses of Pr76gag and the 56,000-, 48,500-, and 32,000-dalton proteins, but not the synthesis of the 47,000-dalton protein. the 56,000-, 48,500-, 47,000-, and 32,000-dalton proteins were not immunoprecipitated by anti-gag, anti-reverse transcriptase, or anti-gp85 antiserum. Two-dimensional peptide maps of the 56,000 and 48,500-dalton proteins indicated that they were unique. In vitro translational products of myeloblastosis-associated virus 1 were also analyzed to aid in the identification of the AMV myb gene product(s); the translational products analyzed included Pr76gag, p60env, and a 56,000-dalton polypeptide which apparently was not identical to the 56,000-dalton AMV translational product, as determined by two-dimensional peptide mapping. Our data indicated that one of these proteins (56,000, 48,500, or 32,000 daltons) may represent the product of the AMV myb gene and, therefore, the putative transforming protein(s) of AMV. (Author abstract) (57 Refs)

STRUCTURE AND LEVELS OF RIBOSOMAL RNA

16. FUNCTIONS OF NUCLEAR BODIES AS REVEALED BY ULTRASTRUCTURAL AUTORADIOGRAPHY AND CYTOCHEMISTRY.

Yasuzumi G, Yabumoto N, Shirai T, Nakai Y, Yasuzumi F
Academy of Medical Technology and Nursing, Hanwa Memorial Hosp., Karita-7, Osaka 558, Japan
Experientia; 37(10):1072-1073 1981

The simple nuclear body containing a few RNA particles appears through the nuclear pores in the cytoplasm, originating from the nucleolus. The complex nuclear body consisting mainly of RNA components is highly active in the incorporation of RNA precursors. Accordingly, the appearance of nuclear bodies may be related either to transport to the cytoplasm of nucleolar components or to the enhancement of rRNA synthesis. (Author abstract) (9 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

17. INHIBITION OF RAT LIVER AMINOACYL-TRNA SYNTHETASES IN VITRO AFTER ACUTE AND CHRONIC AFLATOXIN B1 ADMINISTRATION IN VIVO.

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Chem Biol Interact; 37(1):233-244 1981

In a cell-free system the influence of acute aflatoxin B1 administration on the fractions of the hepatic microsomal translation complex of female rats was examined and compared with the influence of chronic aflatoxin B1 treatment. Polypeptide synthesis determined by [14C]leucine incorporation with a postmitochondrial supernatant was inhibited by 80% 24 hr after acute aflatoxin B 1 administration whereas inhibition was only 17% in animals 30 wk after chronic treatment. After acute aflatoxin B1 administration inhibition of protein synthesis was by 67%, mainly on the polysomal level, whereas inhibition with the pH 5 enzyme was only by 22%. After chronic aflatoxin B1 administration inhibition was by 18%, mainly with the pH 5 enzyme and by only 6% on the polysomes. The inhibition by pH 5 enzyme was further investigated with regard to aminoacyl-tRNA synthetases, components of pH 5 enzyme. Leucine-specific aminoacyl-tRNA synthesis was inhibited by 20% 24 hr after acute and by 12% 30 wk after chronic aflatoxin B1 treatment. Aminoacyl-tRNA synthetase activities in a crude synthetase preparation tested with five amino acids were found to be noncompetitively inhibited. It is concluded that the inhibition of protein synthesis after acute and chronic aflatoxin B1 administration is in part due to decreased aminoacyl-tRNA levels caused by inhibited aminoacyl-tRNA synthetases. (Author abstract) (39 Refs)

18. INHIBITORY EFFECTS OF ANTI-NEOPLASTIC PLATINUM COMPLEXES ON DNA AND RNA POLYMERASES (MEETING ABSTRACT).

Kohl HH, Miller DL
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Clin Chem; 27(6):1066 1981

The present work studies the inhibitory actions of cis-diaminedichloroplatinum II (cis-DDP), trans-diaminedichloroplatinum II (trans-DDP) and other more recently synthesized platinum complexes on both DNA and DNA-dependent RNA polymerases. Soluble and purified enzymes from Escherichia coli were studied in the presence of either a calf-thymus DNA template or Poly (dA-dT). We have also studied a completely mammalian transcription system (intact rat liver nuclei) in a DNA-dependent RNA polymerase assay. Measurements of RNA transcription were made using radioactive guanosine triphosphate while those of DNA synthesis utilized tritiated thymidine triphosphate. Incorporation of radioactivity was measured by counting glass fiber filters using liquid scintillation. Our data indicates that the trans-DDP is far more potent than cis-DDP in inhibiting RNA transcription. Ninety percent inhibition was seen using 10 uM trans-DDP while less than 5% inhibition was seen using cis-DDP. The inhibitions of RNA transcription appear to be due to effects on the polymerase enzyme rather than to effects on the DNA template. DNA synthesis, however, appeared to be inhibited by effects on both the enzyme and the nucleic acid template. (no Refs)

19. EFFECT OF VARIOUS COMPOUNDS ON THE REACTION OF TRIS-(2-CHLOROETHYL)AMINE WITH RIBONUCLEIC ACID IN VITRO AND ON ITS TOXICITY IN MICE.

Szinicz L, Albrecht GJ, Weger N
Institut fur Pharmakologie und Toxikologie, Medizinischen Fakultat der Ludwig Maximilians-Universitat, Nussbaumstrasse 26, D-8000 Munchen 2, W. Germany
Arzneim Forsch; 31(10):1713-1717 1981

The effect of tris(2-chloroethyl)amine (HN-3) on RNA and DNA was investigated spectrophotometrically. The shift in the absorbance spectrum caused by the addition of HN-3 was used to test a variety of compounds for their ability to inhibit RNA alkylation. The effect of HN-3 on the activity of several enzymes was also investigated. The activities of ribonuclease A, desoxyribonuclease I, acetylcholinesterase, diaphorase, glutathione reductase, adenosine desaminase, glyoxalase I, 3-hydroxyacyl-CoA-dehydrogenase, xanthine oxidase, glucose-6-phosphate dehydrogenase, hexokinase and the microsomal N-oxygenation of aniline were not changed by HN-3, whereas the activity of cytochrome-c-reductase exhibited a dose dependent diminution in the presence of HN-3. Of 105 compounds tested only 14, namely, sodium thiosulfate, dithioxanthine, thiosalicylic acid, 1,2,4-triazole-5-thiol, 2-thiocytosine, 2-thiohistidine, 2,3-dithiosuccinic acid, thioglycolic acid, 3-mercapto-D-valine, 6-amino-2-thiouracil, thionicotine amide, dithiothreitol, sodium sulfite, and ergothioneine prevented the alkylation of RNA. All of them also reacted with HN-3 in absence of RNA. No correlation was found between the reaction constant of the reaction compound:HN-3 in the absence of RNA and the concentration of the compound which inhibited RNA alkylation by 50%. The compounds which were effective in vitro were also tested in mice for their ability to reduce HN-3 toxicity in vivo. Only sodium thiosulfate, d-penicillamine, and dithiosuccinic acid were effective. A 3.9fold increase in the LD50 of HN-3 was achieved in mice treated with sodium thiosulfate 3,330 mg/kg ip, a 1.7fold with 2,125 mg dithiosuccinic acid/kg, and a 2fold increase with 2,500 mg/kg d-penicillamine. The compound tested was injected ip 0.5 to 1 min after the sc injection of HN-3. (Author abstract) (33 Refs)

OTHER RELATED STUDIES

20. KAPOSI'S SARCOMA. IV. DETECTION OF CMV DNA, CMV RNA AND CMNA IN TUMOR BIOPSIES.

Boldogh I, Beth E, Huang ES, Kyalwazi SK, Giraldo G
(c/o Huang) Cancer Res. Center, Univ. North Carolina, Chapel Hill, NC, 27514
Int J Cancer; 28(4):469-474 1981

In order to determine whether human cytomegalovirus-(CMV) DNA homologous sequences as well as CMV-specific RNA(s) and antigen(s) exist in tumor biopsies of Kaposi's sarcoma (KS) DNA-DNA reassociation, RNA-DNA in situ cytohybridization and anticomplement immunofluorescence test (ACIF) tests were applied. Three of 10 DNAs extracted from Kaposi sarcoma biopsies contained DNA sequences homologous to radioactively labeled human CMV DNA probe. The amount of CMV DNA in these sarcoma tissues was calculated to range from 0.7 to 1 genome equivalent per diploid cell. The presence of virus-specific RNA was also demonstrated in sections from 5 of 10 tumor biopsies. CMV-determined nuclear antigen(s) (CMNA) present in variable degrees were also demonstrated. In contrast, we could not detect any herpes simple virus type II (HSV-2) or Epstein-Barr virus (EBV) DNA sequences in DNA of these tumor biopsies. Furthermore, there were no detectable HSV-2 or EBV-specific RNA or virus-specific antigens in sections of these biopsies. These results provide new lines of evidence for the relationship between CMV and Kaposi's sarcoma. (Author abstract) (34 Refs)

21. QUANTITATION OF MURINE MAMMARY TUMOR VIRUS-RELATED RNA IN MAMMARY TISSUES OF LOW- AND HIGH-MAMMARY-TUMOR-INCIDENCE MOUSE STRAINS.

Marcus SL, Smith SW, Sarkar NH
Lab. Molecular Virology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Virol; 40(1):87-95 1981

Lactating mammary glands and hormonally induced mammary tumors of BALB/c mice from three geographically separated breeding colonies were examined by molecular hybridization, using murine mammary tumor virus (MuMTV)cDNA representing the entire viral genome to determine the amount of MuMTV-related RNA expressed in these tissues. The RNA extracted from these tissues by the classical sodium dodecyl sulfate-pronase, phenol-chloroform procedure (method 1) contained barely detectable levels of MuMTV-related sequences. In contrast, both normal lactating mammary glands and hormonally induced mammary tumors of these mice were found to contain approx one to two copies of the MuMTV genome per cell by using a new procedure in which the RNA was extracted with guanidine derivatives (method 2). No significant differences in the MuMTV-related RNA content of the BALB/c mammary tissues were observed regardless of their colony of origin. Our results suggest that expression of MuMTV RNA does not change in BALB/c mammary glands during transformation to a malignant state and that MuMTV expression does not play a role in tumorigenesis in these mice. In view of the increased recovery of MuMTV-related RNA from BALB/c mice with method 2, we compared the level of MuMTV RNA expression in lactating mammary glands and mammary tumors of other mouse strains, including C57BL/6 and RIII, using both extraction methods. Yields of MuMTV-related RNA from mammary tissues increased by as much as 35-to 40-fold, using method 2 as compared with method 1. Therefore method 2, involving guanidine derivatives, appears to be the method of choice for MuMTV-related RNA extraction from the mammary tissues of certain strains of mice, particularly those expressing relatively low levels of MuMTV RNA. (Author abstract) (20 Refs)

22. EFFECT OF SANGIVAMYCIN AND XYLOSYLADENINE ON THE SYNTHESIS AND METHYLATION OF POLYSOMAL RIBONUCLEIC ACID IN EHRLICH ASCITES CELLS IN VITRO.

Glazer RI, Hartman KD, Cohen OJ
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Biochem Pharmacol; 30(19):2697-2701 1981

The pyrrolopyrimidine, sangivamycin, and the adenosine analog, xylosyladenine, were examined for their effects on the synthesis and methylation of polysomal RNA in Ehrlich ascites tumor cells in vitro. The synthesis of non-polyriboadenylic acid (non-poly (A)-) and poly(A)-containing RNA was inhibited 50% at concentrations of 7 x 10(-6) M and 3 x 10(-6) M xylosyladenine, respectively, when adenosine deaminase was inhibited with 2'-deoxycoformycin. Sangivamycin inhibited the synthesis of non-poly(A)- and poly(A)RNA by 50% at concentrations of 5 x 10(-5) M and 2 x 10(-5) M respectively. Electrophoretic separation of non-poly(A)RNA into rRNA and tRNA indicated that the inhibitory effects of both drugs were more pronounced on 28S than on 18S rRNA, and that xylosyladenine but not sangivamycin inhibited the synthesis of tRNA. Assessment of the effects of both analogs on the methylation of polysomal RNA revealed that xylosyladenine inhibited the methylation of non-poly(A)- and poly(A)RNA, while sangivamycin only weakly affected the latter species of RNA. Base methylation of the affected species of RNA was inhibited slightly more than 2'-O-methylation by both drugs. These results indicate that sangivamycin is a more selective inhibitor of polysomal RNA in comparison to xylosyladenine under conditions where adenosine deaminase is not a limiting factor. (Author abstract) (24 Refs)

23. CURRENT STATE OF LEUKEMIA PROBLEM.

Gavrilov OK, Shishkov VP, Khokhlova MP
Central Inst. Hematology and Blood Transfusion, Moscow, USSR
Klin Med (Mosk); 59(8):6-10 1981

Current research in the field of etiology, diagnosis, treatment, and prevention of leukemia is reviewed. It was shown that leukemic transformation is associated with an increase in the level of DNA damage, inhibition of messenger RNA synthesis and transport, and inhibition of protein synthesis. In vitro cloning of hematopoietic stem cells in semisolid agar media showed heterogeneity of the group of undifferentiated leukemias. Immunologic methods based on detection of antibodies against bovine leukemia virus showed the presence of oncornavirus infection in the cattle. Development of new antileukemia agents (hexaphosphamide, paphencil, and fotrin) and immunotherapy with viable allogeneic leukemic cells increased duration of survival of children with acute leukemia. (25 Refs) (In RUS)

24. INDUCTION OF ENDOGENOUS MAMMARY TUMOR VIRUS EXPRESSION DURING HORMONAL INDUCTION OF MAMMARY ADENOACANTHOMAS AND CARCINOMAS OF BALB/C FEMALE MICE.

McGrath CM, Prass WA, Maloney TM, Jones RF
Dept. Tumor Biology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
JNCI; 67(4):841-852 1981

Treatment of BALB/c female mice with pituitary isografts, under conditions that established mammary hyperplasia in an anovulatory condition, enhanced mammary tumor development with prior onset of dysplastic foci in lobular parenchyma. Tumor onset began at 8 mo (mean onset time, 18 mo); the 25-mo incidence was 100%. Adenoacanthomatous tumors appeared first. Adenocarcinomas appeared only after more than 14 mo of continuous hormone stimulation. Dysplastic and neoplastic changes occurred while blood levels of the three major mammotropic hormones were physiologic. Murine mammary tumor virus (MuMTV) p28 was detected in all tumors tested, independent of time of tumor appearance or tumor type, although keratinizing cells in adenoacanthomatous tumors did not contribute to MuMTV antigen expression. MuMTV gp52 was detected in only a small fraction of cells in a few tumors. MuMTV RNA contents were above normal in all tumors tested. Neither MuMTV structural antigens nor RNA was induced in normal glands by the same hormone treatment that ultimately resulted in dysplasia and tumor formation and elevated levels of these viral markers in neoplasms. The MuMTV

RNA in all hormone-induced tumors was readily distinguishable in base sequence from standard MuMTV RNA but indistinguishable from MuMTV RNA recovered from lactating mammary glands of BALB/c females carrying only endogenous MuMTV proviruses, suggesting that endogenous MuMTV RNA sequences were induced in hormone-induced neoplasms. RNA indistinguishable from MuMTV sequences present in hormone-induced primary tumors was also detected in multiple genomic equivalents in two independently derived hormone-induced premalignant alveolar hyperplasias. MuMTV p28 was detected, but gp52 was not. The same hormone stimulus that generated 100% tumors in normal glands greatly accelerated tumor development in premalignant hyperplasias but did not amplify MuMTV RNA or antigens in either hyperplasias or the tumors derived from them. B-type virions were not detected in these tissues, in either hypophyseal implant-stimulated or virgin hosts. Cell-free virions were not detected in culture. These data suggest that the replication of MuMTV induced in hormone-induced neoplasms is defective. Details of its expression suggest that if involved in events leading to tumors, its involvement is insufficient cause for those tumors. (Author abstract) (41 Refs)

25. ISOLATION VIA TRANSFECTION OF FELINE LEUKEMIA VIRUSES FROM DNA OF NATURALLY OCCURRING FELINE LYMPHOMAS.

Rosenberg ZF, Crowther RL, Essex M, Jarrett O, Haseltine WA
(c/o Haseltine) Charles A. Danna Cancer Center, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Virology; 115(1):203-210 1981

Feline leukemia viruses isolated via transfection from the DNAs of naturally occurring feline lymphoma tissue were compared with viruses representing the three subgroups of FeLV by host range, subgroup, and RNA fingerprinting analyses. A novel host range was observed for two subgroup A viruses obtained from independent tumors. Two distinct viruses with different host ranges, subgroup specificities, and fingerprint patterns were isolated from a third tumor. Although the tumor tissues used in this study were from unrelated cats, the RNA fingerprints of the four transfected viruses demonstrated striking similarities to one another. Approx 88% of the RNase T1 resistant oligonucleotides present in any one isolate are also present in the other three viruses. The transfected viruses share approx 67% of the RNase T1 resistant oligonucleotides found in FeLV subgroups B or C. However, approx 80% of the RNase T1 resistant oligonucleotides of the new virus isolates are found in common with FeLV A/Glasgow 1. (Author abstract) (25 Refs)

26. AVIAN LYMPHOID LEUKOSIS IS CORRELATED WITH THE APPEARANCE OF DISCRETE NEW RNAS CONTAINING VIRAL AND CELLULAR GENETIC INFORMATION.

Hayward WS, Neel BG, Fang J, Robinson HL, Astrin SM
Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Haematol Blood Transfus; 26:439-444 1981

The virus-related RNA and DNA from 23 avian leukosis virus (ALV)-induced tumors (22 lymphomas, 1 fibrosarcoma) was analyzed. The normal 35S and 21S ALV RNAs were present in many of the lymphomas analyzed. Of the 22 lymphomas, 19 (from 14/17 birds) contained new RNA species not found in uninfected cells or in nontransformed infected cells. In all cases where more than one tumor from the same animal was examined, the same new tumor-specific RNA was found. Class I and II RNAs were not detectable with circular DNA(cDNA)rep, a probe representing the entire viral genome; this indicated that these RNAs contain little, if any, viral information other than the 5' sequences and presumably contain cellular sequences. Class III RNA was detected but the intensity of the bands suggested that only a small portion of the information in these RNAs could be virus-specific. Three of the four tumors analyzed by liquid hybridization contained low or undetectable amounts of 35S and 21S RNAs. In each of these tumors, the levels of RNA detected with cDNAss was at least 20-fold greater than that detected with cDNArep. The ss-containing RNA, presumably representing the new tumor-specific RNAs, was present at levels ranging from 100-1,300 copies per cell. The expression of cellular transformation-specific sequences was studied. New tumor-specific restriction fragments, containing both viral and cellular sequences (JF: junction fragments), were present in lymphoma DNA. All tumors from one bird contained the same tumor-specific JF. New tumor-specific JF were found in all tumors analyzed. Four size classes of JF were found to be common to more than one tumor. The presence of a specific JF correlated with the presence of a new tumor-specific RNA in 8/10 birds in which both RNA and DNA were analyzed. The data suggested that expression of viral genes is not required for maintenance of neop lasia and that lymphoma induction seems to occur only when the provirus integrates at one of a limited number of sites on the host cell chromosome. (25 Refs)

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RNA TRANSCRIPTION/ SYNTHESIS

1. EXPRESSION OF ALPHA-FETOPROTEIN AND ALBUMIN GENES IN A RAT HEPATOMA CELL LINE SY/1/80: EVIDENCE FROM THE NEED OF SPECIES SPECIFIC SERUM FACTORS.

Selten GC, Selten-Versteegen AM, Yap SH
Dept. Medicine, St. Radboud Hosp., Univ. Nijmegen, 6500 HB Nijmegen, The Netherlands
Biochem Biophys Res Commun; 103(1):278-284 1981

The requirement for rat serum factors to express the alphafetoprotein (AFP) and albumin genes in rat hepatoma cell line SY/1/80 is reported. SY/1/80 is a cell line derived from a diethylnitrosamine-induced rat hepatoma. The original tumor

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produces both AFP and globin protein. During in vitro passage of cells in medium supplemented with calf, horse or human serum, the mRNAs for these proteins could not be detected. Supplementation of cultures with rat serum induced the appearance of both AFP and globin mRNAs. While the nature and mechanisms of such species-specific serum factors remains to be elucidated, this observation may explain the inability of cells passaged in calf serum to produced specific proteins in a continuous fashion. (19 Refs)

2. THYROTROPIN-RELEASING HORMONE EXERTS RAPID NUCLEAR EFFECTS TO INCREASE PRODUCTION OF THE PRIMARY PROLACTIN MRNA TRANSCRIPT.

Potter E, Nicolaisen AK, Ong ES, Evans RM, Rosenfeld MG
Div. Endocrinology, Sch. Medicine, Univ. California at San Diego, La Jolla, CA, 92093
Proc Natl Acad Sci USA; 78(11,part2):6662-6666 1981

This report directly documents that a polypeptide hormone can regulate specific gene expression as a consequence of increasing the levels of a primary genomic transcript. The regulation and expression of the prolactin gene was studied in a cell line (GH4) derived from a rat pituitary tumor. These cells respond to addition of the hypothalamic tripeptide, thyrotropin-releasing hormone (TRH; thyroliberin), by elevation of the levels of mature prolactin mRNA and increase in prolactin biosynthesis. The message induction is preceded by, and apparently consequential to, a comparable rapid increase in the nuclear prolactin RNA precursors, including the putative primary transcript. (Author abstract) (38 Refs)

3. CORRELATION BETWEEN MEMBRANE PERMEABILITY AND INDUCTION OF ERYTHROID DIFFERENTIATION BY DMSO IN FRIEND VIRUS TRANSFORMED ERYTHROLEUKEMIA CELLS (MEETING ABSTRACT).

Dube SK, Yamane T
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

How erythroid differentiation is blocked by the Friend virus complex (FVC) or how it is induced by dimethylsulfoxide (DMSO) and other chemicals is not clear. One possibility is that transformation by the FVC leads to an effect on the proerythroblast membrane in such a way that it becomes more permeable to small nutrient molecules and the transformed proerythroblasts thus acquire a proliferative advantage. A prediction of this model would be that DMSO and other inducers reverse this effect. We have measured the uptake of phosphate, leucine, uridine, thymidine and deoxyglucose by Friend erythroleukemic (FEL) cells before and after induction with DMSO. The results showed a dramatic decrease in the uptake of these molecules by induced cells amounting to a drop of about 70% of the control. Our experiments on 32P phosphate incorporation in these cells showed that newly synthesized globin messenger RNA (mRNA) appears in the cytoplasm about 10 hr after addition of DMSO. To determine whether the decrease in membrane permeability temporally coincided with globin mRNA induction, we measured the uptake of phosphate, leucine, etc at hourly intervals after addition of DMSO. A very interesting duality of effect was observed. At first hr time point, there was an increase in the uptake of these molecules and this increase continued up to about 8 hr. After that time the uptake showed first signs of decrease and this was almost concomitant to the initiation of induced globin mRNA synthesis. To further strengthen the interpretation of the uptake data, we used amphotericin B, which is known to increase membrane permeability. We found that if amphotericin B and DMSO are added together, the inducing effect of DMSO is totally wiped out, ie, no globin synthesis is observed. These results, therefore, strongly argue for a correlation between decrease in membrane permeability and induction of erythroid differentiation in FVC transformed proerythroblasts. (no Refs)

4. RNA DEGRADATION DEFECT IN CENTRAL NERVOUS SYSTEM ISOLATES OF VESICULAR STOMATITIS VIRUS.

Hughes JV, Johnson TC
Dept. Microbiology, Univ. Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, KS, 66103
J Gen Virol; 55(part2):253-264 1981

Six temperature-sensitive (ts) mutants of vesicular stomatitis virus (VSV) isolated from the CNS following injection with ts G31 (III) all possessed a post-transcriptional defect, not found in the initial virus, that affects the stability of viral RNA transcripts. Examination of viral RNA metabolism in mouse neuroblastoma (N-18) cells revealed that RNA synthesis of the CNS isolates was decreased considerably at elevated temperatures (up to 80 or 90% at 39 C). In addition, analysis of the RNA transcripts suggested that little if any normal-sized transcripts were made in cells infected with these CNS isolates at either 37 C or 39 C. The RNA deficiencies did not appear to be the result of a temperature-sensitive lability of virion transcriptase as examined by in vitro transcriptase assays. However, when N-18 cells infected with one of the CNS isolates, ts G31 BP, were first preincubated at the permissive temperature of 31 C for 3 hr and then shifted to 39 C, RNA synthesis proceeded at a rate comparable to that of 31 C. The viral mRNA species synthesized following the temperature shift also contained normal-sized tracts of poly(A) RNA, suggesting that neither the viral transcriptase nor its polyadenylate synthetase was thermally labile. However, for any of the six CNS isolates, all species of viral RNA synthesized in cells that were first preincubated at 31 C degraded rapidly when the cells were shifted to 39 C. In contrast little or no RNA degradation of either 42S progeny RNA or mRNA species was detected in the wild-type VSV, ts G31 or three other VSV mutants that are defective in some aspect of viral RNA metabolism: [ts G11 (I), ts G22 (II), ts G41 (IV)]. The appa rent phenotype alteration in the stability of viral RNA in all of these CNS isolates if discussed in terms of the possible genotypic changes that may have occurred as well as the unique CNS disease that accompanies infection by these viruses. (Author abstract) (30 Refs)

5. MECHANISM OF ACTIVATION OF EARLY VIRAL TRANSCRIPTION BY THE ADENOVIRUS E1A GENE PRODUCT.

Nevins JR
Rockefeller Univ., New York, NY, 10021
Cell; 26(2,part2):213-220 1981

Results obtained with certain adenovirus host range mutants (dl312 and hr1) have demonstrated that a functional viral E1A gene is required for the accumulation of early viral mRNA. In this report, it is demonstrated that the failure to accumulate early viral mRNA in E1A mutant-infected cells is due to a lack of transcription of the appropriate transcription units. The E1A gene product appears to enhance transcription of the early transcription units since there is not an absolute requirement for its function. At low multiplicities of infection, transcription from the early transcription units can be detected but at a later time. By increasing the multiplicity of infection, this slow activation of early transcription can be enhanced, even though at this multiplicity all input viruses are still mutant. It was also found that early transcription could be detected in mutant-infected cells if the virus was added to cells in which protein synthesis was inhibited prior to infection. Thus inhibition of cellular protein synthesis can mimic the function of the E1A gene. It is proposed that the role of the E1A gene product in the activation of early viral transcription is to inactivate a cellular factor that prevents transcription from the other early viral promoters. (Author abstract) (48 Refs)

6. CYTOKINETIC AND BIOCHEMICAL EFFECTS OF SANGIVAMYCIN IN HUMAN COLON CARCINOMA CELLS IN CULTURE.

Glazer RI, Hartman KD
NCI, Building 37, Rom 6D28, Bethesda, MD
Mol Pharmacol; 20(3):657-661 1981

The cytokinetic and biochemical effects of sangivamycin (SG) on human colon carcinoma in tissue were studied. Log phase and early plateau phase cells were exposed for 2, 24, and 48 hr to SG and cell viability was determined by soft agar cloning. Brief (2 hr) drug exposure of either log- or plateau-phase cells was not cytotoxic. Prolonging drug exposure to 24 or 48 hr dramatically increased cell lethality; 1 x 10(-6) M SG reduced cell viability of log phase cells by 83% and 97% after 24 and 48 hr of drug exposure, respectively, while cell viability was reduced in plateau-phase cells by 20% and 75%, respectively. Increasing the SG concentration to 1 x 10(-5) M increased cytoxicity only in plateau-phase cells. DNA synthesis was not significantly affected after 2 hr of drug exposure, but precipitously decreased following prolonged incubation with SG for 24 or 48 hr. In contrast, total RNA synthesis was initially inhibited up to 40% after 2 hr of exposure to 1 x 10(-5) SG, but was not reduced much further after longer intervals of drug treatment. RNA synthesis was not significantly inhibited in plateau-phase cells after 48 hr of drug exposure. In contrast, inhibition of non-poly(A)RNA and poly(A)RNA occurred to a degree comparable to that of total RNA in log-phase cells. The time and concentration dependence of SG incorporation into DNA and RNA correlated qualitatively with the effect of SG on cell viability. The incorporation of 3H-SG into poly(A)RNA correlated with the reduction in cell viability observed in log- and plateau-phase cells under comparable conditions. Results indicated that SG produces significant cell lethality to a human colon carcinoma which is generaly refractory to antitumor agents. (15 Refs)

7. IN VIVO RNA SYNTHESIS IN THE HEARTS OF ADRIAMYCIN-TREATED RATS.

Dalbow DG, Jaenke RS
(c/o Jaenke) Dept. Pathology, Colorado State Univ., Fort Collins, CO, 80523
Cancer Res; 42(1):79-83 1982

Data are presented which demonstrate the effect of both acute and chronic Adriamycin treatment on myocardial RNA synthesis in vivo. The results suggest that the inhibition of RNA synthesis is a transient effect following both types of treatment and that the degree and duration of this effect is dose dependent. The data further demonstrate that Adriamycin does not alter the turnover rate of RNA and that both messenger RNA and ribosomal RNA are affected. These results, interpreted in conjunction with pharmacokinetic data, permit speculation on the relationship between acute and chronic Adriamycin treatment as well as cellular ramifications with regard to the protracted, dose-dependent cardiomyopathy. (Author abstract) (19 Refs)

8. COMPARATIVE INHIBITION OF NUCLEAR RNA SYNTHESIS IN CULTURED MOUSE LEUKEMIA L1210 CELLS BY ADRIAMYCIN AND 4'-EPI-ADRIAMYCIN.

Wilson RG, Kalonaros V, King M, Lockwood R, McNeill M
Dept. Biochemistry, Coll. Medicine and Dentistry New Jersey, New Jersey Medical Sch., Newark, NJ, 07103
Chem Biol Interact; 37(3):351-363 1981

Adriamycin and 4'-epi-adriamycin were compared as to their effect on nRNA synthesis. 4'-Epi-adriamycin was a more effective inhibitor than the parent compound of RNA synthesis as measured by incorporation of [3H]uridine. Adriamycin inhibited all three species of nRNA (ribosomal, nonpoly(A)hnRNA, poly(A)hnRNA) to approx the same extent. 4'-Epi-adriamycin on the other hand inhibited the nRNA species in the following order: non-poly(A)hnRNA greater than ribosomal RNA greater than poly(A)hnRNA. The inhibitory effects of both drugs on incorporation of uridine into RNA were reversible at low concentrations (5 ug/ml). (Author abstract) (14 Refs)

9. ACTION MECHANISM OF SAFRAMYCIN A, A LESS IMMUNOSUPPRESSIVE ANTITUMOR ANTIBIOTIC (MEETING ABSTRACT).

Arai T, Ishiguro K, Takahashi K, Mikami Y
Laboratory of Chemotherapy, Chiba Cancer Research Institute, Chiba University, Chiba, Japan
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Saframycin A (SA), which possesses a unique dimeric heterocyclic quinone skeleton and a cyano group, proved to be effective on experimental murine tumor systems as well as on human tumor xenografts in nude mice. Long-lasting cytotoxicity in spite of its rapid absorption to and excretion from the body is one of the novel characteristics of SA. In the studies on the action mechanism of SA, it was revealed that the antibiotic preferentially inhibited both preribosomal RNA and hnRNA to the same degree on account of its interaction with DNA and subsequent inhibition of chain elongation of nascent RNA. SA must be reduced into its active form prior to its interaction with DNA. The isolation and identification of the precursor of SA biosynthesis, decyano-saframycin A or saframycin S, further cast light on the elucidation of SA-DNA interaction. Saframycin S has a alpha-carbinolamine moiety at C-21 position instead of cyano group of SA and hydroxyl group at this position is assumed to be one of the active sites for the binding of saframycins to DNA. The above and other results strongly suggest that C-21 of carbinolamine is covalently attached to exocyclic N-2 of guanine by aminal linkage and the hydrogen bonding between C-15 of SA and 2-keto group of cytosine in the same base pair contributes as the secondary stabilizing force. (no Refs)

10. PRE-CLINICAL AND CLINICAL STUDIES OF NEOTHRAMYCIN (NTM) (MEETING ABSTRACT).

Okada A, Watanabe K, Kusama T, Fujita H, Ogawa K, Kimura K

Tsurumi University, Yokohama, Japan

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

NTM, a new antitumor antibiotics of pyrrolo (1,4) benzodiazepine nucleus, has wide antitumor spectrum such as P-388, AH414 and B16 melanoma, etc. It binds DNA and inhibits DNA dependent RNA and DNA synthesis but its binding activity is slower than other anthramycin or anthracycline antibiotics. A single iv administration of NTM to mice and rabbits at a dose of 10 mg/kg results in plasma level of 19 ug/ml and 43 ug/ml after 5 min and half lives of 12 min and 15 min respectively by high performance liquid chromatography assay method. Its half life is longer than adriamycin, neocarcinostatin and mitomycin C. NTM is distributed well in the kidney, urinary bladder, squamous tissues, lung, spleen and gastro-intestinal tract in mice and rabbits but it disappears rapidly through urine and bile. NTM is partially absorbed from gastro-intestinal tract. The acute toxicity of NTM is lower than that of anthramycins. It has no cardiotoxicity and is weak in local irritability in rabbits. There is no myelo-suppression and no effect to CNS as seen in anthramycins. Phase I and phase II clinical study shows that NTM is effective against squamous cell carcinoma such as esophagus, tongue and lung cancer. Grawitz's tumor and cancerous peritonitis without any side effect except vomiting and nausea up to a dose of 32 mg/m2. The distribution of NTM for human organ will be presented. (no Refs)

11. SELECTIVE EFFECTS OF METAL IONS ON RNA SYNTHESIS RATES.

Niyogi SK, Feldman RP, Hoffman DJ

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Toxicology; 22(1):9-21 1981

Fourteen chloride metal ions were tested in vitro to determine their effects upon Escherichia coli RNA polymerse transcription of calf thymus and T4 phage DNA. Conditions were altered from previously published reports to insure that metal ions were kept in soln (pH 7.4, omissions of 2-mercaptoethanol). Neither overall synthesis nor chain initiation were altered by the new assay conditions. Increasing concentrations of metal ions inhibited transcription in the order Pb2+ greater than Zn2+ greater than Cu2+ greater than Cd2+ greater than Ni2+ greater than Ca2+ greater than Co2+ greater than Mn2+. Be2+ had a stronger inhibitory effect than Cd2+ at low concentrations but less so at higher concentrations. Sr2+ had very little effect. At concentrations of Ca2+, Mg2+, Sr2+, Zn2+, Li+, Na+, and K+, that decreased overall transcription chain initiation was also decreased. These metals are considered to be non-mutagenic and non-carcinogenic. CO2+, MN2+, and Cd2+, metals that are mutagenic and carcinogenic, caused marked stimulation in chain initiation at concentrations that inhibited overall transcription. BeC12 and PbC12, both known carcinogens, caused only a wide range of concentrations that inhibited overall transcription. (42 Refs)

STUDIES OF HETEROGENEOUS NUCLEAR RNA

12. ADENOVIRAL HETEROGENEOUS NUCLEAR RNA IS ASSOCIATED WITH HOST CELL PROTEINS.

Van Eekelen CA, Mariman EC, Reinders RJ, Van Venrooij WJ

Laboratorium voor Biochemie, Katholieke Universiteit Nijmegen, Geert-Grooteplein Noord 21, NL-6525-EZ Nijmegen, The Netherlands

Eur J Biochem; 119(3):461-467 1981

In this study irradiation of intact cells with 254-nm UV light was used to cross-link hnRNA to proteins that are closely associated with it. In this way proteins interacting specifically with hnRNA could be identified excluding the possibility of nonspecific binding of proteins to the RNA during cell fractionation. In uninfected HeLa cells two polypeptides of 41,500 and 43,000 mol wt can be cross-linked very efficiently to hnRNA. Other proteins, with mol wt of 36,000 and 37,000, were covalently linked less effectively. Irradiation of adenovirus-infected cells results in the cross-linking of the same polypeptides to hnRNA. It was found, however, that hnRNA from adenovirus-infected cells contains both viral and host transcripts. Both classes of transcripts are quantitatively associated with the nuclear matrix and can be cross-linked by irradiation with equal efficiency. To determine whether both adenoviral and cellular transcripts are associated with the same proteins, the cross-linked adenoviral hnRNA-protein complexes were isolated by preparative hybridization to adenoviral DNA immobilized on Sepharose. The results show that the purified cross-linked adenoviral hnRNA-protein complexes also contain the host 41,500-Mr and 43,000-Mr proteins as major components. This suggests that in the infected cell adenoviral-specific hnRNA is associated with host proteins and that the structural organization of viral hnRNA-protein complexes in infected cells probably is similar to the organization of host hnRNA in uninfected cells. (Author abstract) (34 Refs)

13. OB ODNOM IZ VOZMOZHNYKH MEKHANIZMOV REGULIATSII ROSTA MNOGOKLETOCHNYKH ORGANIZMOV I EGO PRILOZHENII K PROBLEMAM STARENIIA I KANTSEROGENEZA] [ONE OF THE POSSIBLE MECHANISMS OF GROWTH REGULATION OF MULTICELLULAR ORGANISMS AND ITS APPLICABILITY TO THE PROBLEMS OF AGING AND CARCINOGENESIS.

Mustafin AM

Kazakh Inst. Oncology and Radiology, Alma-Ata, USSR

Usp Sovrem Biol; 92(2):261-277 1981

The role of nucleoproteins containing redundant DNA or heterogenous RNA in regulation of the growth of multicellular organisms is reviewed, with special emphasis on the mechanisms of aging and carcinogenesis. It is suggested that malignant transformation is associated with intensive tumor cell death and thus with accumulation of degradation products, including fragments of redundant DNA and RNA. (165 Refs) (In RUS)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

14. REGULATION OF GENE EXPRESSION BY TUMOR PROMOTERS. III. COMPLEMENTATION OF THE DEVELOPMENTAL PROGRAM IN MYELOID LEUKEMIC CELLS BY REGULATING MRNA PRODUCTION AND MRNA TRANSLATION.

Hoffman-Liebermann B, Liebermann D, Sachs L
Dept. Genetics, Weizmann Inst. Science, Rehovot 76100, Israel
Int J Cancer; 28(5):615-620 1981

Regulation of gene expression has been analyzed in different clones of mouse myeloid leukemic cells treated with the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA), the macrophage- and granulocyte-inducing protein MGI, and combined treatment with TPA and MGI. Two-dimensional gel electrophoresis was used to measure changes in the rate of synthesis of specific proteins and in the amount of corresponding translatable mRNAs assayed in the reticulocyte cell-free translation system. TPA induced different subsets of differentiation-associated protein changes in the different clones and the degree of response to TPA was not necessarily related to the degree of response to MGI. It is shown that TPA can induce protein changes either by inducing the synthesis of new mRNA, by increasing or decreasing the amount of pre-existing mRNA, or by modulating the translation of a constant amount of mRNA. Combined treatment with TPA and MGI resulted in an enhancement of protein changes induced by MGI or TPA alone and induced differentiation-associated protein changes not induced by either compound separately in differentiation-defective clones. This complementation of gene expression appeared to be due to each compound inducing functions not induced by the other, so that the combined treatment resulted in new gene expression. Complementation also occurred at the level both of mRNA production and of mRNA translation. It is suggested that the ability of TPA to regulate gene expression at the level of mRNA production and mRNA translation and to complement changes in gene expression induced by other compounds such as MGI are important functions for its role as a tumor promoter. (Author abstract) (34 Refs)

15. IN VITRO TRANSLATION OF HYPOXANTHINE/GUANINE PHOSPHORIBOSYLTRANSFERASE MRNA: CHARACTERIZATION OF A MOUSE NEUROBLASTOMA CELL LINE THAT HAS ELEVATED LEVELS OF HYPOXANTHINE/GUANINE PHOSPHORIBOSYLTRANSFERASE PROTEIN.

Melton DW, Konecki DS, Ledbetter DH, Hejtmancik JF, Caskey CT
Howard Hughes Medical Inst. Lab., Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 77030
Proc Natl Acad Sci USA; 78(11,part2):6977-6980 1981

Antibody specific for the native form of Chinese hamster hypoxanthine/guanine phosphoribosyltransferase (HPRT; IMP:pyrophosphate phosphoribosyltransferase, EC 2.4.2.8) was used to detect the synthesis of HPRT protein in a rabbit reticulocyte lysate translation system primed with mRNA from Chinese hamster tissues and cultured cells. Electrophoretic analysis of the immunopurified products from the translation of mRNA from wild-type and a series of mutant Chinese hamster cells indicated that HPRT synthesis in vitro qualitatively and quantitatively corresponded to synthesis in vivo. The translation system was used to identify two mRNA sources producing high levels of HPRT protein: Chinese hamster brain and a mouse neuroblastoma HPRT revertant cell line, NBR4. Translation of NBR4 mRNA generated 25-50x more HPRT protein than mRNA from wild-type cells. The basis for HRPT overproduction is considered in view of an X chromosome alteration found in NBR4 cells. (Author abstract) (20 Refs)

16. ESTRADIOL STIMULATES SYNTHESIS OF A MAJOR INTRACELLULAR PROTEIN IN A HUMAN BREAST CANCER CELL LINE (MCF-7) (MEETING ABSTRACT).

McGuire WL, Edwards DP, Adams DJ
Department of Medicine and Oncology, University of Texas Health Sciences Center, San Antonio, TX
Fifth International Symposium of the Journal of Steroid Biochemistry, July 13-15 , 1981, Puerta Vallarta, Jalisco, Mexico. Journal of Steroid Biochemistry 80 pp., 1981.

Estradiol was found to selectively stimulate synthesis of a 24,000 dalton cytosol protein, provided cell growth was inhibited by antiestrogen prior to addition of estradiol (estrogen 'rescue'). Another growth rescue model, produced by withdrawing serum from the medium to inhibit cell growth and then stimulating cells by readdition of serum, failed to stimulate increased synthesis of the 24K protein, implying that the estradiol effect is not a non-specific result of growth rescue. Adaptation of a double isotope ratio method to the reticulocyte cell-free translation assay has revealed two estrogen-regulated messenger RNA (mRNA) in the human breast cancer cell line MCF-7. These mRNA's code for proteins of 24,000 and 54,000 daltons as analyzed on SDS polyacrylamide gels. (no Refs)

17. CONTROL OF ADENOVIRUS EARLY GENE EXPRESSION: ACCUMULATION OF VIRAL MRNA AFTER INFECTION OF TRANSFORMED CELLS.

Persson H, Katze MG, Philipson L
Dept. Microbiology, Biomedical Center, S-751 23 Uppsala, Sweden
J Virol; 40(2):358-366 1981

We studied the accumulation of viral mRNA in the presence of inhibitors of protein synthesis in an adenovirus Type 5-transformed cell line (line 293 cells). An analysis of the endogenous viral mRNA's and proteins revealed that only early regions 1A and 1B were expressed in uninfected 293 cells. However, viral mRNA's from early regions 2, 3, and 4, as well as mRNA's from early regions 1A and 1B, accumulated in 293 cells after infection with adenovirus Type 2. Cells treated with anisomycin before infection showed a drastic enhancement of mRNA from early region 4 compared with drug-free controls. This increase in viral mRNA was detected by using filter hybridization, S1 endonuclease mapping, and in vitro translation. The rate of transcription of early region 4 nuclear RNA also increased significantly in the presence of anisomycin. In contrast to the results with early region 4, the levels of cytoplasmic mRNA's from early regions 2 and 3 did not increase in cells treated with inhibitors. These results suggested that multiple virus encoded controls operate on the early regions of the adenovirus genome. (Author abstract) (31 Refs)

18. MAPPING OF RNAS TRANSCRIBED FROM ADENOVIRUS TYPE 12 EARLY AND VA RNA REGIONS.

Saito I, Sato JI, Handa H, Shiroki K, Shimojo H
(c/o Shimojo) Inst. Medical Science, Univ. Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108, Japan
Virology; 114(2):379-398 1981

We have defined the sizes and map positions of adenovirus type 12 (Ad12) cytoplasmic RNAs produced during the early and intermediate phases of infection using the nuclease S1-gel technique. S1-protected [32P]DNAs were analyzed in conventional neutral and alkaline agarose gels as well as in a two-d imensional agarose gel system. In Ad12 early regions 1A, 1B, 2, 3, and 4, were identified four, three, one, five, and five mRNA species, respectively. These mRNAs formed family structures, commonly shared a limited variety of 3' and/or 5' end positions and multiple splicing patterns. Most mRNAs showed all possible combinations of terminal positions and splicing patterns. In spite of these complex features, a remarkable similarity was observed between Ad12 and Ad2 mRNA structures in each early region. However, several differences were observed in these early regions, especially in early region 3. Only a single species of Ad12 VA RNA was detected near 30 map units, as with Ad2 VA RNAI. (Author abstract) (25 Refs)

19. EXPRESSION OF ADENOVIRUS TYPE 2 LATE GENES IN HELA CELLS INFECTED WITH ADENOVIRUS TYPE 2 OR ADENOVIRUS TYPE 2-SIMIAN VIRUS 40 HYBRID VIRUSES.

Lawrence CB
Dept. Cell Biology, Baylor Coll. Medicine, Texas Medical Center, Houston, TX, 77030
J Virol; 40(2):610-614 1981

The relative levels of expression of the five 3'-coterminal mRNA families encoded in the 16.4 to 99 map unit transcription unit of adenovirus Type 2 (Ad2) are determined in part by the frequency of utilization of five possible polyadenylation sites. The possibility that polyadenylation frequencies at these sites may be regulated was tested by examining the expression of the fiber (polypeptide IV) gene in cells infected with nondefective (ND) Ad2-simian virus 40 hybrid viruses which express a sixth late mRNA family. Both the relative rate of fiber protein synthesis and the relative abundance of fiber mRNA were normal in cells infected with the hybrid viruses Ad2+ND1, Ad2+ND2, or Ad2+ND4. (Author abstract) (23 Refs)

20. EARLY RNA OF ADENOVIRUS TYPE 3 IN PERMISSIVE AND ABORTIVE INFECTIONS.

Groff DE, Daniell E
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
J Virol; 40(2):620-624 1981

Early adenovirus Type 3 cytoplasmic polyadenylated RNAs from HeLa and BHK-21 cells were detected and mapped on the viral genome by gel blotting and hybridization techniques. The sizes and locations of the 16 adenovirus Type 3 RNAs were identical in the two cell types, although relative molarities of the various RNA species differed. Each of the early adenovirus Type 3 RNAs was associated with polysomes in both cell types, suggesting that the abortive infection of hamster cells does not result from a defect in early adenovirus Type 3 mRNA biosynthesis. No RNAs from regions transcribed late in infection of permissive cells were detected in BHK-21 cells. (Author abstract) (26 Refs)

21. THE STABILITY OF EARLY ADENOVIRUS MRNA IS CONTROLLED BY THE VIRAL 72 KD DNA-BINDING PROTEIN.

Babich A, Nevins JR
Rockefeller Univ., New York, NY, 10021
Cell; 26(3,part1):371-379 1981

H5ts125, a temperature-sensitive mutant of adenovirus type 5, is restricted to the early phase of infection when grown at the nonpermissive temperature. One phenotype of the virus is the overproduction of early viral mRNA at the nonpermissive temperature relative to levels found in wild-type-infected cells, although normal levels are found at the permissive temperature. We have analyzed this phenomenon for the production of RNA from two specific early viral transcription units, E1A and E1B. Transcription rates from both of these regions were found to be the same in ts125-infected cells as in wild-type-infected cells at the nonpermissive temperature. However, when the cytoplasmic stabilities of the E1A and E1B mRNAs were measured in wild-type- and ts125-infected cells, it was found that at the nonpermissive temperature, the RNAs were 3 to 5x more stable in a ts125 infection than in a wild-type infection. Since the mutation in ts125 maps to the gene for the 72 kd DNA-binding protein, these results imply that a functional 72 kd protein is required for the rapid turnover of early viral mRNA in wild-type-infected cells, indicating that the abundance of early viral mRNA is controlled by the 72 kd DNA-binding protein. (Author abstract) (54 Refs)

22. NUCLEOTIDE SEQUENCES OF 5' TERMINI OF ADENOVIRUS 2 EARLY TRANSFORMING REGION E1A AND E1B MESSENGER RIBONUCLEIC ACIDS.

Hashimoto S, Wold WS, Brackmann KH, Green M

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Biochemistry; 20(23):6640-6647 1981

The major 5'-terminal RNase T1 oligonucleotides derived from human adenovirus type 2 (Ad2) early regions E1a and E1b were characterized and sequenced. Poly(A+) polyribosomal RNA was isolated from Ad2-infected KB cells cultured 10 h in the presence of cycloheximide, the 5'-terminal m7Gppp was removed, and the 5'-OH of the penultimate 2'-O-methylated nucleoside was labeled with [gamma-32P]ATP by using polynucleotide kinase. 5'-32P-labeled poly(A+) RNA was hybridized to EcoRI-A, HpaI-E, and HpaI-C and to cloned fragments representing map positions 0-4.5, 4.5-8, 8-10.7, 8-17, and 17-31.5. Fragment-specific mRNA was digested with RNase T1, the resulting oligonucleotides were resolved by two-dimensional paper electrophoresis-homochromatography, and the 5'-terminal methylated oligonucleotides were characterized by nuclease P1 digestion and two-dimensional thin-layer chromatography. Two major 5'-terminal RNase T1 oligonucleotides were obtained from EcoRI-A-specific mRNA; these were characterized by RNase T2 digestion and two-dimensional thin-layer chromatography and were sequenced by partial nuclease P1 digestion and electrophoresis-homochromatography. These two oligonucleotides were mapped to E1a and E1b, respectively, by analysis of E1a- and E1b-specific mRNA. Their sequences are as follows: E1a, m7G pp(m6)AmC(m)UCUUGp; E1a,m7Gppp(m(6))AmC(m)UCUUGp; E1b,m7Gppp(m(6))AmC(m)AUCUGp, in which the methylations shown in parentheses are partial. The E1a 5'-terminal oligonucleotide was found as a minor component of E1b mRNA, implying that mRNAs exist with both E1a and E1b sequences. Five other minor 5'-terminal oligonucleotides were observed in E1 mRNA, implying that transcription initiation is not always precise. Sequences corresponding to these two 5' termini were found at nucleotide positions 498-504 (E1a) and 1699-1705 (E1b) in the Ad2 DNA sequence, positions where the 5'-terminal region of E1a and E1b mRNAs has been mapped by nuclease gel analysis and electron microscopic visualization. (50 Refs)

23. THE EXPRESSION OF VIRUS-SPECIFIC NUCLEOTIDE SEQUENCES IN ROUS SARCOMA CELLS.

Ratovitski EA, Shaposhnikov JD, Bobrov YF, Kuznetsov OK
Petrov Res. Inst. Oncology, USSR Public Health Ministry, Leningrad, 188 646, USSR
Neoplasma; 28(4):413-422 1981

Poly(A)-enriched virus-specific mRNAs (v-mRNA) are revealed in the subcellular fractions (nuclei, mitochondria, polyribosomes and cytosol) from chicken and hamster Rous sarcoma cells. The qualitative and quantitative differences in v-mRNA populations from permissive and non-permissive tumors are shown. The sedimentation analysis of v-mRNAs allowed to ascertain the presence of three molecular classes of v-mRNA in nuclei and cytoplasm of chicken Rous sarcoma cells (35S, 28S and 22S, and 35S, 26-28S and 20S, respectively). While two size classes (33S and 20S) are shown in hamster Rous sarcoma nuclei, only 24S v-mRNa is revealed in the cytoplasm of its tumor tissue. Thus, the oncovirus gene expression is restricted in the non-permissive tumor cells, unlike that of the permissive chicken Rous sarcoma cells, both in the level of transcription, and in the processing and transfer v-mRNAs from nucleus to cytoplasm. The virus gene function peculiarities in the tumors of birds and mammals are discussed. (Author abstract) (32 Refs)

STRUCTURE AND LEVELS OF RIBOSOMAL RNA

24. LINEAR DENSITY OF NUCLEIC ACID MOLECULES AS A FUNCTION OF DENATURING AND SPREADING CONDITION IN ELECTRON MICROSCOPIC ANALYSIS.

Korb J, Stokrova J, Heine UI
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, Flemingovo n. 2, CS-166 10 Prague 6, Czechoslovakia
Stud Biophys; 84(3):195-206 1981

The behavior of single stranded PhiX 174 DNA, 18S and 28S ribosomal RNA, and avian myeloblastosis (AMV) and vesicular stomatitis (VSV) viral RNA was analyzed under different denaturing and spreading conditions during electron microscopic visualization. Contour lengths and apparent linear density of the DNA and RNAs depended on both denaturation and spreading conditions. (28 Refs)

25. THE COMPARATIVE EFFECTS OF 5-AZACYTIDINE AND DIHYDRO-5-AZACYTIDINE ON POLYSOMAL RNA IN EHRLICH ASCITES CELLS IN VITRO.

Lin HL, Glazer RI
NCI, Building 37, Room 6D28, Bethesda, MD, 20205
Mol Pharmacol; 20(3):644-648 1981

To determine if differences in cytotoxicity between azacytidine (AZC) and dihydro-5-azacytidine (DHAZC) result from their effects on the posttranscriptional processing of nuclear (n) RNA or from modification of the translational activity of drug-substituted messenger (m) RNA, the synthesis of polysomal ribosomal (r) RNA, transfer (t) RNA, and mRNA [poly(A)RNA], and the translational activity of AZC- and DHAZC-modified poly(A)RNA were determined in Ehrlich ascites cells in vitro. A significant difference was observed in the potency of these drugs as exhibited by their relative inhibitory effects on the synthesis of rRNA in Ehrlich ascites cells in vitro. At 10(-5) M AZC, 28 S and 18 S rRNA synthesis was inhibited 65% and 35%, respectively, whereas 10(-4) AZC inhibited both 28 S and 18 S rRNA by 70%. In contrast, 50% inhibition of 28 S and 18 S rRNA was produced only at 10(-3) M DHAZC. The amount of cytidine analogue incorporated into a particular species of RNA was not proportional to its effect on the synthesis or function of that RNA. Although rRNA and 4 S RNA contained equivalent amounts of AZC, only the synthesis of rRNA was inhibited. Similarly, poly(A)RNA contained the highest specific radioactivity of labeled AZC and DHAZC. Results suggested that the primary site of action of AZC and DHAZC appears to be related to its inhibitory effect on rRNA. The relative differences in potency between AZC and DHAZC as antitumor agents correlates closely with their respective inhibitory effects on rRNA synthesis and their incorporation into this species in RNA. (30 Refs)

26. EFFECTS OF GROWTH STATE AND 3H LABELING LEVEL ON RNA TURNOVER IN WI-38 FIBROBLASTS AND HELA CELLS.

Sameshima M, Schlessinger D
Tokyo Metropolitan Inst. Medical, Science, 3-18 Honkomagome, Bunkyo-ku, Tokyo 113, Japan
Radiat Res; 88(2):333-342 1981

The basis for differential rates of RNA turnover in various cell types was investigated. It was found that the rate of turnover of RNA prelabeled with 3H-uridine in WI-38 cells varied with the amount of 3H-label incorporated, with the cell density of the cultures, and with the arrest of growth induced by senescence. The half-life of cells in cultures at higher density was 3.9 days, and about 7.6 days in culture diluted four fold until cells were nearly confluent, at which time the half-life decreased to 4.2 days. When the levels of 3H-uridine incorporation were too low to slow cell growth, the half-life of rRNA was consistently longer in cultures at lower density. The half-life of rRNA was the same in senescent cells diluted either 1-or 16-fold (3.0 days). The half-life of rRNA of established HeLa M and mouse L cells was 15 and 40 days, respectively. For cultures of WI-38 cells labelled with 0.01, 0.3 and 8.0 cpm/cells, the half-lives of RNA were 10.5, 8.0 and 5.0 days. Comparable levels of 3H incorporation had little effect on the rate of RNA turnover in several established cell lines, including SV-40 transformed WI-38 cells and HeLa cells. (19 Refs)

STRUCTURE AND LEVELS OF TRANSFER RNA

27. PROSTAGLANDIN HYDROPEROXIDASE-MEDIATED 2-AMINO-4-(5-NITRO-2-FURYL)[14C]THIAZOLE METABOLISM AND NUCLEIC ACID BINDING.

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Cancer Res; 41(12):4961-4966 1981

Prostaglandin hydroperoxide-mediated metabolism and binding of 2-amino-4-(5-nitro-2-furyl)[14C]thiazole ([14C]ANFT) metabolite to nucleic acids and proteins were investigated with rabbit bladder transitional epithelial and solubilized ram seminal vesicle microsomes. Metabolism was assessed by spectrophotometric and radiochemical techniques. Substrate and inhibitor studies are consistent with both metabolism and binding of [14C]ANFT occurring by the prostaglandin hydroperoxidase activity of prostaglandin endoperoxide synthetase. The ratio of the rates of [14C]ANFT product formation is approx 3:7:10 (organic soluble:non-trichloroacetic acid precipitable: trichloroacetic acid precipitable) over a wide range of arachidonic acid concentrations. Approx 2 and 1% of the total [14C]ANFT metabolized binds to transfer RNA and DNA, respectively. The metabolite isolated from the organic phase had a chromatographic profile and UV spectra different from authentic ANFT. If transfer RNA or DNA is added at the end of a 5-min incubation, no binding to nucleic acids was observed. The demonstration of prostaglandin hydroperoxidase-mediated covalent binding to nucleic acids is consistent with the involvement of this enzyme in 5-nitrofuran-induced bladder carcinogenesis. (Author abstract) (44 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

28. ACTIVATION OF PURIFIED HEPATOMA RNA POLYMERASE I BY HOMOLOGOUS PROTEIN KINASE NII.

Duceman BW, Rose KM, Jacob ST
Dept. Human Genetics, Yale Univ. Coll. Medicine, New Haven, CT, 06510
J Biol Chem; 256(21):10755-10758 1981

We have recently purified a cyclic nucleotide-independent, heparin-sensitive nuclear protein kinase (NII) from Morris hepatoma 3924A and demonstrated an apparent relationship of this kinase to the two subunits (Mr = 42,000 and 24,600) of RNA polymerase I. When homogeneous protein kinase NII was recombined with purified homologous RNA polymerase I containing limiting quantities of endogenous kinase, RNA synthesis was stimulated as much as five-fold during a 90-min incubation. The enhanced RNA synthesis was due to an increase in the av RNA chain length; protein kinase did not alter the number of RNA molecules synthesized by the polymerase. Phosphorylation of RNA polymerase occurred at serine and threonine moieties. Unlike the NII kinase, purified homologous NI kinase did not phosphorylate RNA polymerase I and, as a result, did not alter transcription. These data indicate that (1) RNA polymerase I is activated by protein kinase NII, (2) endogenous protein kinase NII remaining with highly purified RNA polymerase I does not fully phosphorylate RNA polymerase I in vitro, and (3) protein kinase NII is capable of regulating RNA polymerase I activity by preventing premature termination of RNA chains. (Author abstract) (21 Refs)

29. LYSOSOMAL ENZYME ACTIVITIES AND RNA TURNOVER RATES IN GROWING AND NONGROWING WI-38 AND HELA CELLS.

Saha BK, Sameshima M, Sameshima F, Schlessinger D
Dept. Microbiology and Immunology, Washington Univ. Sch. Medicine, St. Louis, MO, 63110
In Vitro; 17(9):816-824 1981

Activities of three lysosomal enzymes - acid RNase, N-acetyl-beta-D-glucosaminidase and acid phosphatase - were determined during the growth cycles of WI-38 and HeLa cells, as well as in radiation-arrested WI-38 cells. In confluent and growth-arrested cultures of WI-38 cells, the lysosomal RNase increased six- to sevenfold; glucosaminidase, four- to five-fold; and phosphatase, two- to threefold. In HeLa cells, the lysosomal enzymes also increased in confluent cultures, but less than twofold; and the RNase level increased only transiently. In both WI-38 and HeLa cells, the rate of RNA breakdown also increased as cultures approached confluency. The rate of turnover of RNA, like the level of acid RNase, was higher in WI-38 cells than in HeLa cells (4 day half-life compared to 8 day). The increase in acid RNase could be prevented by incubation of cells in NH4Cl, but the rate of turnover in the presence of NH4Cl increased just as much when cells became confluent or stopped growth. The content of acid RNase could be changed more than 10-fold without altering the rate of RNA turnover. It is suggested that the increase in enzyme level is more important for possible autophagy or increased digestion of engulfed RNA, rather than for normal RNA turnover, when growth stops. (Author abstract) (26 Refs)

OTHER RELATED STUDIES

30. SMALL NUCLEAR RNAS IN CELLULAR GROWTH AND DIFFERENTIATION. I: METABOLIC ALTERATIONS SEEN IN FRIEND ERYTHROLEUKEMIA CELLS.

Kuncio GS, Goldstein L
Dept. Molecular Biology, Univ. Colorado, Boulder, CO, 80309
J Cell Physiol; 109(2):235-241 1981

The distribution of small nuclear RNAs (snRNAs) in Friend virus-transformed murine erythroleukemia cells (FLC) was analyzed under a variety of physiological conditions with electrophoretic techniques. The presence of at least 15 snRNAs distinct from ribosomal 5.8 Svedberg (S) or 5 S were demon strated. Nuclei from rapidly growing, quiescent, and terminal differentiated (and quiescent) cell contained the same complement of snRNAs. All snRNAs were synthesized in FLC irrespective of the physiological state of the cell; however, significant quantitative differences in the labeling pattern of snRNA were seen. Progression from rapid growth to quiescent or from a proerythroblast to a normoblast was accompanied by changes in the pattern of snRNAs in the nucleus. As cells progress from a rapid growth state to quiescence, a substantial reduction in the level of all snRNAs, except 4.5 S, occurred. The most dramatic reductions occurred in the amount of the nucleolar-specific snRNAs U3 and species 2, and in the differential reduction of the U1 species. A similar pattern was seen in differentiated cells, but with more marked decreases for U2 and 4.55 snRNAs. These results indicate that snRNA metabolism is apparently regulated in a developmentally significant fashion, both in association with changes in proliferative capacity of cells and with changes in gene expression that occur during terminal differentiation. (37 Refs)

31. DETECTION OF NUCLEIC ACID SEQUENCES IN CERVICAL TUMORS.

McDougall JK, Galloway DA, Crum C, Levine R, Richart R, Fenoglio CM
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Gynecol Oncol; 12(2,part2):S42-S55 1981

Our results suggest that HSV RNA is present in abnormal cells in a significant proportion of cervical tissue specimens containing intraepithelial neoplasia and that it is only rarely detected in sections of normal cervical epithelium. A proliferation of atypical basal-type cells and their continued persistence through the more mature upper layers is the first indication of dysplasia and CIN in cervical epithelium, and it is in these proliferating cells that evidence of HSV RNA can be found. The results of localizing an HSV-2 antigen (ICSP 11-12) closely parallel the in situ hybridization results. About 30% of patients with dysplasia (CIN I and II) have detectable antigen. It is interesting to note that the incidence of detectable antigen decreased to 12% in patients with carcinoma in situ, but was demonstrable in 20% of patients who had microinvasive or invasive squamous cell lesions. (Author abstract) (52 Refs)

32. CYTOKINETIC AND BIOCHEMICAL EFFECTS OF 5-IMINODAUNORUBICIN IN HUMAN COLON CARCINOMA IN CULTURE.

Glazer RI, Hartman KD, Richardson CL
NCI, Building 37, Room 6D28, Bethesda, MD, 20205
Cancer Res; 42(1):117-121 1982

The semisynthetic anthracycline, 5-iminodaunorubicin (IM), was investigated to see whether modification of the benzoquinone moiety to produce a drug with low free radical potential would alter the cytotoxic and biochemical characteristics of this drug in comparison to Adriamycin (ADR), an a gent with high free radical potential. Cell viability was measured in human colon carcinoma (HT-29) cells by soft-agar cloning. Upon exposure of either log-phase or early plateau-phase cells for 2 hr to IM or ADR, a threshold exponential cell lethality curve was obtained. Prolonging drug exposure to 24 hr produced an exponential decline in cell survival and a marked reduction in viability of both log-phase and early plateau-phase cells. Inhibition of DNA synthesis in log-phase cells after 2 and 24 hr of exposure to IM and ADR paralleled the increased cell lethality produced by the drugs. In contrast, total RNA synthesis was not inhibited by IM, whereas ADR impaired both RNA and DNA synthesis. Nuclear rRNA synthesis was not significantly inhibited following 24 hr of exposure to 10(-7) M ADR or IM but was inhibited by 85 and 35% at 10(-6) M ADR or IM, respectively. The affinity of IM and ADR for HT-29 DNA was measured in vitro by displacement of acridine orange binding and was found to be similar for both analogs. These studies suggest that the cytotoxicity of IM and ADR results from the interactions of these drugs with DNA. (Author abstract) (20 Refs)

33. TWO INDUCERS OF CELL DIFFERENTIATION ENHANCE THE 2'5' OLIGOADENYLATE SYNTHETASE ACTIVITY IN MSV TRANSFORMED CELLS.

Besancon F, Bourgeade MF, Justesen J, Ferbus D, Thang MM
Institut de Biologie Physico-Chimique, 13, rue Pierre et Marie Curie, 75005 Paris, France
Biochem Biophys Res Commun; 103(1):16-24 1981

It is reported that butyrate and dimethyl sulfoxide (DMSO), which are also effective inducers of Friend and neuroblastoma cell differentiation are both inducers of the 2'5'oligoadenylate synthetase activity (OAS) in Maloney sarcoma virus (MSV)-transformed murine BALB/c cells. After incubation in the presence of 1 milliM butyrate, a linear increase of OAS activity was observed with time. OAS levels stayed the same in control cultures in the presence or absence of serum. In the butyrate treated cells, however, in the absence of serum OAS activity was about 4-fold increased over levels obtained in the presence of serum. No antiviral activity could be found, and it was thus assumed that observed changes in OAS activity could not be due to the induction of interferon. OAS activity was found to be dependent upon the presence of double stranded RNA as previously shown for the interferon-induced enzyme. When interferon was added to the butyrate-treated cells the level of enzyme activity and the inhibition of viral multiplication were higher than in the non-treated cells. A report of enhanced antiviral and antitumor action of interferon by butyrate has been previously published. DMSO pretreatment produced similar results to butyrate pretreatment. (28 Refs)

34. CHARACTERIZATION BY NUCLEIC ACID HYBRIDIZATION OF HTLV, A NOVEL RETROVIRUS FROM HUMAN NEOPLASTIC T-LYMPHOCYTES.

Reitz MS, Poiesz BJ, Ruscetti FW, Gallo RC
Natl. Cancer Inst., Bethesda, MD, 20014
Haematol Blood Transfus; 26:515-516 1981

Cyclic DNA (cDNA) and 70S RNA were prepared from the novel human neoplastic T-lymphocyte retrovirus HTLV. These probes were used to determine (1) degree of relatedness to other viruses, (2) whether or not HTLV is endogenous, and (3) whether related sequences can be found in other human tissues. HTLV cDNA hybridized 90% to its own 70S RNA; it did not hybridize significantly to a variety of retroviruses including murine and feline leukemia and sarcoma viruses, baboon endogenous virus, squirrel monkey retrovirus, Mason-Pfizer virus, bovine leukemia virus, RD114 endogenous cat virus, murine mammary tumor virus, and avian myeloblastosis virus. Low (5-10%) levels of hybridization were achieved with 70S from woolly monkey virus and gibbon ape leukemia virus. No HTLV hybridization was obtained with DNA or RNA from normal human peripheral blood T-lymphocytes, with DNA from non- neoplastic autopsy tissues or peripheral blood samples from patients with acute myelogenous leukemia, chronic myelogenous leukemia, or chronic lymphocytic leukemia. DNA from 1/3 acute lymphocytic leukemias (ALL) and 1/2 Sezary syndrome peripheral blood samples hybridized a significant 20-25% of HTLV cDNA. The positive ALL was T-cell. HTLV appears to be a novel retrovirus isolate not endogenous to humans. Results suggest that it is associated with T-cell lymphomas and leukemias of mature cell type. (1 Ref)

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RNA TRANSCRIPTION/ SYNTHESIS

1. ENDOCRINOLOGICAL ASPECTS OF BREAST PHYSIOLOGY (MEETING ABSTRACT).

Robyn C
Human Reproduction Research Unit, Universite Libre de Bruxelles, Hopital Saint-Pierre, Brussels, Belgium
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A2 1981

Growth of the mammary gland is discontinuous; a first wave occurs at puberty under the influence of sex steroids, and the parenchymal breast tissue differentiates into a ductular-lobular-alveolar system. Growth slowly continues with each menstrual cycle up to the age of 30-35. A second major wave of growth takes place during pregnancy. Estrogens, progesterone and prolactin with variable relative potencies induce proliferation and differentiation of alveolar epithelial stem cells and control arborization of the ductular-lobular system. The interplay of the three hormones seems to be essential for optimal and balanced growth of the mammary tissue. From mid-pregnancy, the secretory differentiation of the alveolar stem cells is induced, predominantly under the influence of prolactin in syner-

HE 20.3173/2:

gism with metabolic hormones: this involves Messenger (m)-RNA synthesis for the production of milk proteins and enzymes. However, during pregnancy most of the secretory effects of prolactin are suppressed and lactation does not occur: in vitro, progesterone suppresses the prolactin effects of casein m-RNA synthesis. After delivery, progesterone, estrogens and placental lactogen abruptly drop and prolactin induces full secretory activity and milk release. Oxytocin is required for milk ejection. Prolactin and oxytocin are released by neuroendocrine reflexes initiated by suckling. Prolactin does not appear to be essential for maintaining lactation. In mothers nursing for 2 yr or more, hyperprolactinemia persists for 15-18 mo; it is associated with infertility due to anovulation or corpus luteum deficiency. The decline in serum prolactin levels seen in the mothers after 18 mo of lactation is not associated with a decline in milk yield, at least when considering the amount of milk per feeding. Finally, the sequence of the endocrine events controlling full differentiation of the breast tissue and the timing of their occurrence seem to be of decisive importance in the resistance of the mammary epithelium to carcinogenic agents. (no Refs)

2. IN VITRO TRANSCRIPTION OF ADENOVIRUS.

Fire A, Baker CC, Manley JL, Ziff EB, Sharp PA
Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Virol; 40(3):703-719 1981

A series of recombinants of adenovirus DNA fragments and pBR322 was used to test the transcriptional activity of the nine known adenovirus promoters in a cell-free extract. Specific initiation was seen at all five early promoters as well as at the major late promoter and at the intermediate promoter for polypeptide IX. The system failed to recognize the two other adenovirus promoters, which were prominent in vivo only at intermediate and late stages in infection. Microheterogeneity of 5' termini at several adenovirus promoters, previously shown in vivo, was produced in the in vitro reaction and indeed appeared to result from heterogeneous initiation rather than 5' processing. To test for the presence of soluble factors involved in regulation of mRNA synthesis, the activity of extracts prepared from early and late stages of infection was compared on an assortment of viral promoter sites. Although mock and early extracts showed identical transcription patterns, extracts prepared from late stages gave 5-to 10-fold relative enhancement of the late and polypeptide IX promoters as compared with early promoters. (Author abstract) (43 Refs)

3. STRUCTURE OF THE BABOON ENDOGENOUS VIRUS GENOME: NUCLEOTIDE SEQUENCES OF THE LONG TERMINAL REPEAT.

Tamura T, Noda M, Takano T
Dept. Microbiology, Keio Univ. Sch. Medicine, Shinjuku-ku, Tokyo, Japan
Nucleic Acids Res; 9(23):6615-6626 1981

The entire nucleotide sequence of the long terminal repeat (LTR) of baboon endogenous virus (BaEV) M7 was determined, which consisted of 554 base pairs (bp). At both ends of the LTR, 13 bp sequences, AAATGAAAAGTAA and TGATTCTAACATC, were detected to be inverted repeats. The structure with these inverted repeats resembles those of other retroviruses and transposable elements. A Hogness box, TATAAAA, and a putative poly(A)-addition signal, AGTAAA, were present within the right-hand half of the LTR, where the initiation and termination of the viral RNA synthesis seems to occur in the integrated BaEV genome. The primer-binding site of at least 14 bp long was found just outside of the LTR where the strong stop DNA started, and the primer for reverse transcription in BaEV seemed to be tRNA-Pro. Several structural features are commonly detected in the LTRs of BaEV and other retroviruses. Our studies suggest that BaEV has evolved from a common ancestor with other mammalian Type C viruses. Close relationships between BaEV and a feline endogenous virus, RD114, are demonstrated. (Author abstract) (33 Refs)

4. STRUCTURE, STABILITY, METHYLATION, EXPRESSION AND GLUCOCORTICOID INDUCTION OF ENDOGENOUS AND TRANSFECTED PROVIRAL GENES OF MOUSE MAMMARY TUMOR VIRUS IN MOUSE FIBROBLASTS.

Hynes NE, Rahmsdorf U, Kennedy N, Fabiani L, Michalides R, Nusse R, Groner B

Kernforschungszentrum Karlsruhe, Institut fur Genetik und fur Toxikologie, Postfach 3640, D-7500 Karlsruhe, W. Germany

Gene; 15(4):307-317 1981

A sequence of mouse genomic DNA containing an endogenous mouse mammary tumor virus (MMTV) provirus, which was isolated by molecular cloning in lambda vector phage, has been reintroduced into cultured mouse L cells, using the thymidine-kinase (TK) cotransfection technique. Transfection of mouse cells with a lambda-MMTV recombinant DNA molecule, MMTV RNA expressed in the GR-40-transfected L cells, stability of transfected MMTV DNA in LTK+GR-40+ cells, hypomethylation of MMTV-transfected DNA, and MMTV-specific proteins in LTK+GR-40+-tranfected cells are discussed. Individual cell clones that acquired the transfected MMTV proviral DNA have been isolated. The transfected DNA remains stable in these cells and does not become methylated. It is transcribed into MMTV RNA, and the transcription is stimulated by glucocorticoid hormones. Results suggested that the transfected TK DNA and the MMTV proviral DNA are linked. Clone GR-40 contains a region of DNA which mediates the response to glucocorticoid. (39 Refs)

5. A CASCADE OF ADENOVIRUS EARLY FUNCTIONS IS REQUIRED FOR EXPRESSION OF ADENO-ASSOCIATED VIRUS.

Richardson WD, Westphal H

Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, Bethesda, MD, 20205

Cell; 27(1,part2):133-141 1981

One measurable biological activity of early adenovirus genes is their ability to promote growth of the defective adeno-associated virus, AAV. We have identified an ordered sequence of communications among the early genes of adenovirus Type 2 (Ad2) that results in expression of the helper activity. We purified DNA fragments and mRNAs corresponding to early Ad2 regions E1, E2A, E3 and E4 and injected them via glass capillaries into AAV-infected cells. DNAs were placed in the nucleus, mRNAs in the cytoplasm. AAV DNA and proteins synthesized in response to the injected Ad2 nucleic acids were extracted from as few as 100 cells and identified by gel electrophoresis. Our results reveal a cascade of early Ad2 gene regulation, E1 to E2A to E4, with E4 providing the helper effect for AAV. (Author abstract) (51 Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

6. A NEW ADJUVANT TREATMENT WITH POLYADENYLIC-POLYURIDYLIC ACID IN OPERABLE BREAST CANCER.

Lacour F, Lacour J, Spira A, Michelson M, Delage G, Petit JY, Viguier J
Laboratoire d-Immunologie, Institut Gustave-Roussy, 16 bis Avenue Paul Vaillant-Couturier, F-94800 Villejuif, France
Recent Results Cancer Res; 80:200-206 1982

Adjuvant treatment with polyadenylic-polyuridylic acid poly A-poly U was tested in 300 patients with operable breast cancer who had all received the same locoregional treatment. They were randomized into two groups; 155 patients receiving 30 mg poly A-poly U iv once a wk for 6 wk and 145 controls. Overall survival was significantly improved in the poly A-Poly U group (p less than 0.05). The most striking difference (p less than 0.03) was observed in the group of positive node patients, who had a 5-yr relapse-free actuarial survival rate of 71% vs 47% in the controls. (Author abstract) (14 Refs)

7. SEQUENCES AT THE CAPPED 5'-ENDS OF POLYOMA VIRUS LATE REGION MRNAS: AN EXAMPLE OF EXTREME TERMINAL HETEROGENEITY.

Cowie A, Tyndall C, Kamen R
Transcription Lab., Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London WC2A 3PX, England
Nucleic Acids Res; 9(23):6305-6322 1981

We have localized with respect to the genomic DNA sequence the capped 5'-termini of polyoma virus late region mRNAs. A minimum of fifteen different purine termini were found within a 94 base pair region (66.36 to 68.12 map units, nt 5075-5168) immediately preceding the sequence determining the late region mRNA leader repeat (1-3). The most common termini occur at nearly every possible purine within a 25 bp sequence proximal to the leader repeat unit. These do not bear the usual positional relationship to a sequence resembling the 'TATA' box consensus. Deletion mutants lacking minor cap sites and sequences upstream from the principal cap sites were viable. A deletion mutant lacking one of the principal cap sites formed sma ll plaques, while a slightly larger deletion further impinging on the principal cap site region was non-viable. The principal cap sites, which we assume to be transcriptional initiation points, are included in a DNaseI hypersensitive region of polyoma virus chromatin. (Author abstract) (51 Refs)

8. COMPLEMENTARY SELECTED ALKYLATION OF POLY(A)-FRAGMENTS OF MRNA IN KREBS ASCITES TUMOR CELLS.

Zarytova VF, Ivanova EM, Karpova GG, Knorre DG, Pichko NP, Rait AS, Stefanovich LE
Inst. Organic Chemistry, Novosibirsk, USSR
Bioorg Khim; 7(10):1512-1522 1981

A method of selective alkylation of poly(A) sequences of messenger RNA in Krebs ascites carcinoma cells is described. 2',3'-0-[4-(N-methyl-N-2-chloroethylamino)] [14C]benzylidene was shown to penetrate tumor cells and to alkylate the nucleic acids. (30 Refs) (In RUS)

9. CYCLIC AMP REGULATION OF LACTATE DEHYDROGENASE. QUANTITATION OF LACTATE DEHYDROGENASE M-SUBUNIT MESSENGER RNA IN ISOPROTERENOL- AND N6,O(2)'-DIBUTYRYL CYCLIC AMP-STIMULATED RAT C6 GLIOMA CELLS BY HYBRIDIZATION ANALYSIS USING A CLONED CDNA PROBE.

Miles MF, Hung P, Jungmann RA
(c/o Jungmann) Cancer Center, Dept. Molecular Biology, Northwestern Univ. Medical Sch., Chicago, IL, 60611
J Biol Chem; 256(23):12545-12552 1981

We have cloned DNA complementary to mRNA coding for rat C6 glioma cell lactate dehydrogenase M-subunit. Double-stranded DNA complementary to a portion of lactate dehydrogenase mRNA was inserted into the Pst I site of plasmid pBR322 by the dC.dG tailing technique and amplified in Escherichia coli HB101. A recombinant plasmid containing lactate dehydrogenase cDNA was identified by colony hybridization to a cDNA prepared from partially purified lactate dehydrogenase mRNA and by hybridization-selected translation. The recombinant plasmid (pRLD42) contains a 680 nucleotide insert of lactate dehydrogenase mRNA. Hybridization of nick-translated pRLD42 to glioma cell poly(A)+RNA separated on agarose gel and transferred to nitrocellulose exhibited Mr = 5.9 x 10(5) for lactate dehydrogenase mRNA. Furthermore, Northern blot analysis of RNA from unstimulated and isoproterenol-stimulated glioma cells indicated a two-fold increase of lactate dehydrogenase mRNA molecules in stimulated cells. The two-fold increase of lactate dehydrogenase mRNA was confirmed by RNA-excess kinetic hybridization using pRLD42 DNA and poly(A)+RNA from unstimulated isoproterenol-, and dibutyryl cAMP-stimulated glioma cells. These data demonstrate that isoproterenol and dibutyryl cAMP cause an increase of the number of lactate dehydrogenase M-subunit mRNA molecules in glioma cells which, in part, determines the extent of synthesis of the lactate dehydrogenase M-subunit. (Author abstract) (56 Refs)

10. THE REGULATION OF PROTEIN SYNTHESIS IN HEART MUSCLE UNDER NORMAL CONDITIONS AND IN THE ADRIAMYCIN-CARDIOMYOPATHY.

Zahringer J
Med. Klinik I, Klinikum Grosshadern, Marchioninistr. 15, D-8000 Munchen 70, W. Germany
Klin Wochenschr; 59(23):1273-1287 1981

The regulation of cardiac protein synthesis, in particular messenger-RNA (mRNA) and polyribosome metabolism, has been investigated in normal rat heart muscle and in the adriamycin-cardiomyopathy by using newly developed methods for the isolation, characterization and in vitro translation of cardiac polyribosomes and mRNA. (94 Refs)

11. VIRAL MESSENGER RNAS IN SIX LINES OF ADENOVIRUS-TRANSFORMED CELLS.

Lewis JB, Mathews MB
(c/o Mathews), Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, NY, 11724
Virology; 115(2):345-360 1981

We have compared the proteins translated in vitro using virus-specific mRNA from six lines of adenovirus-transformed cells (F4, F17, F19, REM, T2C4, and 293) with those made using RNA from productively infected cells. The mRNAs for proteins E1A-58K, 54K, 48K, and 42K, and for E1B-15K, were detected in all cell lines and for E1B-57K in at least five of the lines. Neither of the minor E1A mRNAs (for proteins 25K and 28K) found under specific conditions in infected cells were found in any transformed cell line. Two cell lines, F4 and T2C4, contained small amounts of other mRNAs encoded within region E1B including in the latter case one not detected in infected cells. The lines F4, REM, and T2C4 contain at least some E4 mRNAs, again including in the latter case one not detected in infected cells. T2C4 cells also contain E3 mRNAs, E2A-72K protein mRNA, and two E2B mRNAs, although the 32B proteins are not identical to any found in infected cells. The F19 and T2C4 lines express mRNAs encoded between 11 and 17 map units, the 'IVa2 region', but do not include the mRNA for polypeptide IVa2 itself. Some early mRNAs, including the 'immediate early' mRNAs, have not been detected in any of these lines of transformed cells: nor did the cell lines contain any mRNAs found exclusively at late times during productive infection. Comparison of these results with the properties of the cells tentatively suggest a correlation (although not necessarily causal) between the expression of additional viral genes and increased tumorigenicity. (Author abstract) (58 Refs)

12. THE STRUCTURES OF THE SPLICED MRNAS ENCODING POLYOMA VIRUS EARLY REGION PROTEINS.

Treisman R, Cowie A, Favaloro J, Jat P, Kamen R
(c/o Kamen) Transcription Lab., Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
J Mol Appl Genet; 1(2):83-92 1981

Polyoma (Py) virus early region messenger (m)RNAs synthesized during productive infection of mouse 3T6 cells were characterized at the nucleotide level. In the establishment of basic structures, nuclease S1-resistant hybrids formed between tsa 'shift-up' cytoplasmic polyadenylated RNA and Py DNA restriction fragments which span the entire early region were analyzed by one- and two-dimensional agarose gel electrophoresis. The two splice donors and two splice acceptors were positioned more precisely by high resolution S1-gel mapping with terminally labeled DNA probes and polyacrylamide gels. The nucleotide sequences across the three splice joints were established by cloning and sequencing partial complementary (c)DNA copies of the mRNAs. The present data, in combination with previously described data on the polyadenylated 3'-end and detailed analysis of the capped 5' ends, complete the description of a family of differentially spliced mRNAs able to encode the known early region gene products, small-T, middle-T, and large-T proteins. (31 Refs)

13. THE 2.2 KB E1B MRNA OF HUMAN AD12 AND AD5 CODES FOR TWO TUMOR ANTIGENS STARTING AT DIFFERENT AUG TRIPLETS.

Bos JL, Polder LJ, Bernards R, Schrier PI, Van den Elsen PJ, Van der Eb AJ, Van Ormondt H
Dept. Medical Biochemistry, Sylvius Lab., Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Cell; 27(1,part2):121-131 1981

By nucleotide sequence analysis and S1 nuclease mapping we have determined the structural organization of early region E1b of Ad12. We have also revised the nucleotide sequence of the E1b region of Ad5. Both regions have an identical structural organization and show considerable homology at the nucleotide level. The major tumor antigens (Ad12, 19 and 54 kilodaltons [kd]); Ad5, 21 and 55 kd are encoded in two overlapping reading frames. A single mRNA of 2.2 kilobases codes for both these proteins, depending on which AUG triplet serves as the start codon: the 19-21 kd protein initiates at the 5'-proximal AUG; the 54-55 kd protein initiates at the second AUG in another reading frame. Peptide mapping shows that the small and large tumor antigens do not share common tryptic peptides, in accordance with the nucleic acid sequence data. In addition, the 19-21 kd protein can also be synthesized from a one kilobase mRNA. Finally, the gene for the Ad12 analog of protein IX is characterized. (Author abstract) (48 Refs)

14. TRANSLATION OF LYMPHOCYTE MRNA INTO BIOLOGICALLY-ACTIVE INTERLEUKIN 2 IN OOCYTES.

Bleackley RC, Caplan B, Havele C, Ritzel G, Mosmann TR, Farrar JJ, Paetkau V
(c/o Paetkau) Dept. Biochemistry, Univ. Alberta, Edmonton, Alberta T6G 2H7, Canada
J Immunol; 127(6):2432-2435 1981

A variant line of murine T lymphoma EL4 produces high levels of the lymphokine Interleukin 2 (IL 2) when it is stimulated with phorbol myristate acetate. We have extracted poly A+ RNA from the stimulated cells and injected it into Xenopus laevis oocytes. The injected oocytes synthesize a material with biological and biochemical properties of murine IL 2. Namely, it stimulates the continued growth factor of a cloned, cytotoxic T-cell line (the T-cell growth factor assay) and it chromatographs on a gel filtration column (G-100) with IL 2 produced by the stimulated EL4 line. The RNA responsible for the biologic activity sediments with markers of 11 to 12S in a sucrose gradient. The IL 2 produced by injected oocytes from a given preparation of mRNA is about 1% of the amount produced by the EL4 cells stimulated originally with phorbol myristate acetate. When RNA is extracted and purified from unstimulated EL4 cells it does not induced IL 2 production in oocytes. We conclude that IL 2 is essentially protein in nature, that the protein is coded for by poly A+ mRNA, and that the amount of this mRNA increases significantly after stimulation of the variant EL4 cells with the inducer phorbol myristate acetate. (Author abstract) (19 Refs)

15. SYNTHESIS OF AN UNSPLICED CYTOPLASMIC MESSAGE BY AN ADENOVIRUS 5 DELETION MUTANT.

Carlock L, Jones NC
(c/o Jones) Dept. Biological Sciences, Purdue Univ., West Lafayette, IN, 47907
Nature; 294(5841):572-574 1981

A mutant of adenovirus 5 (dl502) which contains a deletion within early region Ela and prevents splicing of the normal Ela transcripts is described. Mapping of cytoplasmic RNA isolated from wild-type and dl502-infected HeLa cells indicated that an unspliced Ela message is synthesized and accumulates in the cytoplasm of dl502-infected cells. Comparison of the Ela-generated autoradiograph bands from wild-type and dl502 RNA preparations showed that the unspliced Ela product from dl502 accumulates in the cytoplasm to 25-50% of the levels of wild-type Ela products. It is thought unlikely that the unspliced message could have resulted from nuclear leakage. Two phenotypic properties of dl502 indicated that a defective, partially functional, Ela gene product was being synthesized. Increased synthesis of dl502, which is defective for growth on HeLa cells, was attributed to the synthesis of a partially functional Ela gene product required for productive growth, by dl502. The second indicator was detection of transcripts from other regions of the genome, although seen at reduced levels. The results indicated that an unspliced region Ela transcript accumulates in the cytoplasm of dl502-infected cells; splicing and the removal of intron sequences are not necessary prerequisites to the production of stable, cytoplasmic RNA from this particular gene. (27 Refs)

OTHER RELATED STUDIES

16. TUMOR ANGIOGENESIS FACTOR (TAF) IN CULTURED CELLS DERIVED FROM CENTRAL NERVOUS SYSTEM TUMORS IN HUMANS.

Matsuno H
Dept. Neurosurgery, Neurological Inst. Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan
Neurol Med Chir (Tokyo); 21(7):765-773 1981

Quantitative and qualitative assays were made of tumor angiogenesis factor (TAF) produced by cell lines derive from human CNS tumors. Supernatants were obtained from confluent cultures of five glioma cell lines (GCL), four primary cultures of meningiomas (PCM), one metastatic tumor cell line (MT), and one skin fibroblast cell line (SFC). TAF activities of supernatants corresponding to cell counts of 1.9-2.5 x 10(6) cells were assayed on chick chorioallantoic membrane. TAF activity was found in supernatants from 3/5 GCL, 3/4 PCM, and the MT cultures. SFC produced no TAF activity. Analysis of TAF from one GCL showed that it was destroyed by ribonuclease or heating at 80 C for 30 min, but not by exposure to trypsin, deoxyribonuclease, or heating at 56 C for 30 min. TAF may therefore be a macromolecule related to tumor RNA. Exposure of GCL to 2,500 rads did not destroy TAF activity. TAF activity varied from one cell line to another, with primary or early passaged cultures producing greater activity than long-term cultures. (20 Refs)

17. HEREDITARY ALTERATIONS IN TUMOR-HOST RELATIONSHIP.

Palacios O, Kubinski H
(c/o Kubinski) Univ. Wisconsin, 183 Medical Sciences Building, Madison, WI, 53706
Cancer Lett; 14(3):323-328 1981

Effects of exposure in utero to Ehrlich ascites cells (EH mice) on the adult mouse response to the tumor were examined. EH mice did not exhibit greater survival than controls after challenge with Ehrlich ascites cells, but they did not initially suffer the wt loss or undergo the toxic shock shown by control animals. EH mice had RNA fractions 12 hr after treatment that resembled ribosomal RNA; the RNA fraction of control mice had a base ratio resembling DNA, indicating no injury to cells growing in EH mice but considerable injury to those growing in control mice. No temporary decrease in cytoplasmic RNA was observed in cells obtained from EH mice. In contrast to EH mice, control mice showed a marked decrease in mitochondria in the periportal area and in the centrolobular zone 12-48 hr after inoculation. Such changes in reactivity were hereditary. (14 Refs)

18. INFLUENCE OF PYRAZOFURIN ON THE TOXICITY AND ANTITUMOR ACTIVITY OF FLUORINATED PYRIMIDINES IN VIVO.

Johnson RK, Howard WS, Faucette LF, Wodinsky I, Clement JJ
Arthur D. Little, Inc., Cambridge, MA
Adv Enzyme Regul; 19:309-333 1981

We undertook to evaluate the interaction of pyrazofurin (PF) with another important pyrimidine antimetabolite, 5-fluorouracil (5-FU). 5-FU can be anabolized to the nucleoside monophosphate by three pathways, directly via phosphoribosylation by orotate phosphoribosyltransferase (EC 2.4.2.10), or via the salvage pathways, by either uridine phosphorylase (EC 2.4.2.3) and uridine kinase or thymidine phosphorylase (EC 2.4.2.4) and thymidine kinase (EC 2.7.1.21). One might expect that depletion of pyrimidine nucleotides by PF might enhance the anabolism of 5-FU and allow for greater incorporation of 5- FU into RNA and/or lead to higher levels of 5-fluoro-2'-deoxyuridylate (FdUMP) with subsequent greater inhibition of thymidylate synthase (EC 2.1.1.45). This was, however, not the case. On the contrary, PF markedly decreased the toxicity of 5-FU and blocked its antitumor activity in some tumors as well. With the closely related compound, 5-fluorouridine (FUR), the interaction with PF was the opposite; there was a marked enhancement of both toxicity and antitumor activity similar to that seen with 5-ACr. (46 Refs)

19. THE IMMUNOREGULATORY CHARACTERISTICS OF THE LACTIC DEHYDROGENASE VIRUS (LDV), A COMMON CONTAMINANT OF TUMORS.

Isakov N, Segal S, Feldman M
Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel
Cell Mol Biol; 27(2/3):83-96 1981

A tumor-enhancing and antibody increasing spleen cell-associated factor originating in Lewis lung carcinoma (3LL)-bearing C57BL/6 mice was identified as the lactic dehydrogenase virus (LDV). A potent immunoregulating factor was obtained only following the inoculation of LDV-infected but not LDV-free tumor cells. The observed augmentation of humoral responses by an acute infection with LDV was found to be fully correlated with the ability of the virus to replicate and establish a persisting infection in the host. LDV caused an augmented humoral response in all mouse strains tested (causing a life-long viremia), but failed to influence the humoral response in rats, which are an LDV-resistant species. We found that although an infection with LDV causes a polyclonal B-cell activation it does not affect all of the different B-cell clones and in the presence of a specific antigenic stimulus it preferentially triggers the IgG2 subclass of antibody-secreting B cells. An acute LDV infection causes a substantial suppression of cell-mediated immunity functions and a delayed thyroid allograft rejection was demonstrated in infected mice. Since mononuclear phagocytes, which are the target cells of LDV, play an important role in cellular immune responses, we tested the immunogenic antigen-presenting capacity of LDV-infected macrophages, using a system in which in vitro reactivation of memory T cells is dependent upon effective specific antigen presentation by macrophages. We found that the antigen presentation capacity of macrophages from acute LDV-infected mice is impaired. These results may contribute to a better understanding of the ways in which mammalian RNA viruses may act as immunomodulators. (Author abstract) (42 Refs)

20. STRUCTURE-ACTIVITY RELATIONSHIPS OF ANTHRACYCLINES RELATIVE TO CYTOTOXICITY AND EFFECTS ON MACROMOLECULAR SYNTHESIS IN L1210 LEUKEMIA CELLS.

Matsuzawa Y, Oki T, Takeuchi T, Umezawa H
Central Res. Lab., Sanraku-Ocean Co., Ltd., 4-9-1 Johnan, Fujisawa, Kanagawa 251, Japan
J Antibiot (Tokyo); 34(12):1596-1607 1981

The effects of 92 anthracycline compounds on the growth and DNA, RNA and protein synthesis of L1210 leukemia cells were studied in relationships to their structures and antitumor activity. The hydroxyl groups at C-1, C-2, C-4, C-6, and C-11 on aglycones have significant relationships to the in vitro potency. Compounds lacking the hydroxyl group at C-6 or containing the methoxyl group at C-6 are lower in their cytotoxicity and RNA and DNA synthesis-inhibiting activity than those containing the C-6 hydroxyl group. The hydroxyl group at C-2 did not influence the in vitro potency, but the hydroxyl group at C-1 and/or C-11 enhanced the potency. The activity which prolongs the life span of L1210-bearing mice was decreased by an hydroxyl group at C-1 or C-11, although the effective doses were lowered. In compounds which are different at C-4, in vitro potency increased in the following series: deoxy greater than hydroxy greater than methoxy. The side chain at C-9 in aklavinone- and daunomycinone-glycosides produced slight influence on cytotoxicity and on the activity which inhibits RNA and DNA synthesis in intact cells. Ethyl, isopropyl and acetonyl derivatives at C-9 had an equal potency. The methyl derivative had the least activity. A 10-carbomethoxy group in the S-configuration decreased the inhibitory activity on RNA synthesis. The removal of this group at C-10 resulted in a marked reduction in cytoxicity and in the activity which inhibits nucleic acid synthesis. The amino function either on the aglycone or on the sugar moiety was essential for in vitro activity. Compounds having an alkylamino group at C-3' were more potent in vitro than those with a primary amino group, although these groups produced different effects in in vivo activity, depending on each anthracycline. Disaccharides and trisaccharides were more potent in vitro than monosaccharides. The length of the sugar chain did not correlate with in vivo antitumor activity. (31 Refs)

21. DEXAMETHASONE INDUCTION OF THE INTRACELLULAR RNAS OF MOUSE MAMMARY TUMOR VIRUS.

Robertson DL, Varmus HE
Graduate Section Biochemistry, Dept. Chemistry, Brigham Young Univ., Provo, UT, 84602
J Virol; 40(3):673-682 1981

We have studied the kinetics of dexamethasone induction of mouse mammary tumor virus (MMTV) RNAs and proteins in virus-infected rat XC cells and GR mouse mammary tumor cells. A detectable increase in viral RNA in infected XC cells was present within 10 min after hormone addition, and half-maximal induction was achieved in less than 2 hr. The increase in viral RNA concentration was apparent first in nuclear RNA and later in the cytoplasm. Within the first 15 min of induction, only genome-sized RNA (35S, 7.8 kilobases) was present in augmented amounts. whereas the major subgenomic RNA (24S, 3,8 kilobases) did not appear until at least 30 to 60 min postinduction. The sequential appearance of these RNAs, the probable mRNA's for the gag and env proteins, paralleled the order of appearance of the gag and env proteins, respectively, after hormone treatment. An additional species of viral RNA (20S, 2.5 kilobases) was detected during these induction experiments, but the role of this RNA is not known. Both subgenomic RNAs contain sequences derived from both the 5' and 3' termini of genomic RNA and are presumably spliced. After dexamethasone induction of infected XC cells, we detected two smaller env-related proteins which were not found in full hormone induction. The functional role of these smaller proteins is not known. A previously reported smaller species of RNA (13S, 1.0 kilobase) did not appear to be induced and was shown to be cellular rather than viral in origin. In the fully induced infected XC and GR mammary tumor cells, the only viral RNAs present were the 35S and 24S RNAs. In addition, mammary tumors contained only these two viral RNAs. Thus, tumor cells appear to contain only the viral RNAs which direct the synthesis of the gag, pol, and env proteins of the virion. (Author abstract) (43 Refs)

22. METABOLISM OF VIRAL RNA IN MURINE LEUKEMIA VIRUS-INFECTED CELLS: EVIDENCE FOR DIFFERENTIAL STABILITY OF VIRAL MESSAGE AND VIRION PRECURSOR RNA.

Messer LI, Levin JG, Chattopadhyay SK
Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, Bethesda, MD, 20205
J Virol; 40(3):683-690 1981

Molecular hybridization techniques were used to examine the stability of viral message and virion precursor RNA in murine leukemia virus-infected cells treated with actinomycin D. Under the conditions used, viral RNA synthesis was inhibited, but viral protein synthesis continued, and the cells produced noninfectious particles (actinomycin D virions) lacking genomic RNA. Analysis of total RNA in virions revealed that the amount of hybridizable viral RNA decreased steadily after the addition of actinomycin D and by 8 hr was 10% of the control value. Studies on fractionated viral RNA showed that this low level of hybridization is due to residual 70S RNA in the virion population. The results indicated that viral RNA which is destined to be encapsidated into virions has a half-life of approx 3 to 4 hr. In contrast, other intracellular virus-specific RNA molecules appeared to be quite stable and persisted for a long period of time, with a half-life of at least 12 hr. These observations support the idea that two independent functional pools of 35S viral RNA exist within the infected cell: one serving as message and the other as precursor to virion RNA. The existence of two viral RNA pools was further documented by the finding that 12 hr after the addition of actinomycin D, when virion precursor RNA was depleted, 35S and 21S viral mRNA sp ecies could be identified in polyribosomal RNA as well as in total polyadenylated cell RNA. Surprisingly, 35S mRNA declined more rapidly than did 21S mRNA, which appeared to be increased in amount. (Author abstract) (48 Refs)

23. RNA/DNA RATIO DURING UNBALANCED CELL GROWTH INDUCED BY ANTITUMOR AGENTS (MEETING ABSTRACT).

Traganos FN, Darzynkiewicz Z, Melamed MR
Investigative Cytology Laboratory, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY, 10021
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Use of the metachromatic dye, acridine orange, to stain cells in suspension for flow cytometry allows for the simultaneous measurement of DNA and RNA content in individual cells. The relative RNA content as a function of total cellular nucleic acid content (RNA/DNA + RNA) is constant and unique for particular cell lines under optimal growth conditions. This ratio can be estimated for each cell cycle compartment (ie, G1A, G1B, S, and G2 + M). Changes in the growth rate or the addition of antitumor drugs induces characteristic changes in the RNA/DNA ratio either evenly throughout--or at a particular phase of--the cell cycle. Under such conditions, measurement of cellular DNA and RNA content provides a sensitive assay of any deviation from balanced cell growth. Examples of unbalanced growth caused by suboptimal culture conditions or as a result of incubation with aclacinomycin, ICRF

159, vinblastine, ellipticine, dihydroxyanthraquinone and hydroxyurea are presented. (no Refs)

24. IN VITRO TRANSFER OF LEUKEMIC CELL IMMUNITY WITH XENOGENEIC IMMUNE RNA (MEETING ABSTRACT).

Weber B, Guerci O, Pierrez J, Marbache E, Belotti O, Janot C, Schooneman F
No affiliation given
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Lymphocyte transformation assays (LTA) were performed to demonstrate the transfer of leukemic cell immunity to healthy human lymphocytes in vitro with RNA extracted from lymphoid organs of sheep immunized with leukemic cells. RNA was extracted by the hot phenol method. RNA rich extracts were assessed for RNA, DNA and protein concentration and analyzed by band sedimentation analytic ultracentrifugation on prep UV scanner. Soluble blast cell antigens were obtained by 3M KCl extraction. Normal lymphocytes previously incubated with RNA (90 g/10(5) cells) were cultured in presence of leukemic antigen. Tritiated thymide uptake was measured by liquid scintillation counting. Controls consisted of cultures of RNA treated or untreated lymphocytes with antigen, no antigen or phytohemagglutinin (PHA). Twelve sets of assays were achieved. Two types of results were observed. In 5 cases, the tritiated thymide uptake of RNA treated lymphocyt es increased significantly when cultured with leukemic antigen at increasing protein concentration up to a threshold value and then decreased. No significant increase in tritiated thymide was observed when lymphocytes were not previously incubated with RNA. In all these cases RNA rich extracts contained RNA 12 S sedimentation fraction. In 7 cases RNA treated lymphocytes have no increase of tritiated thymide uptake with respect to ultracentrifugation no 12 S was found in 5 cases and was degraded in 2 cases. RNA was demonstrated not to have blocking or mitogenic properties in our experimental condition. Lymphocytes gave good reactivity as assessed by lymphocyte transformation assay in presence of PHA. The role of immune RNA in mediating tumor immunity is controversely regarded. We have pointed out lymphocytes need RNA 12 S to get sensitized. The effect of RNase treatment will be presented. (no Refs)

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- CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION 21-22
- OTHER RELATED STUDIES 23-29

RNA TRANSCRIPTION/ SYNTHESIS

1. SPECIFIC IN VITRO INITIATION OF TRANSCRIPTION ON THE ADENOVIRUS TYPE 2 EARLY AND LATE EII TRANSCRIPTION UNITS.

Mathis DJ, Elkaim R, Kedinger C, Sassone-Corsi P, Chambon P
(c/o Chambon), Institut de Chimie Biologique, Strasbourg 67085, Cedex, France
Proc Natl Acad Sci USA; 78(12):7383-7387 1981

Three transcription units are present in the adenovirus Type 2 region EII. Transcription units EIIaE and EIIaL encode the mRNA for the 72,000-dalton DNA binding protein, early and late in the lytic cycle, respectively, and transcription unit EIIb encodes the mRNA for the protein that binds to the 5' termini of adenovirus DNA. By using a cell-free transcription system in the presence of purified RNA polymerase B (or II), we have obtained specific initiation of transcription from both the EIIaE promoter, which does not contain a T-A-T-A box, and the EIIaL promoter, which does. In addition, we have identified a new EII T-A-T-A box promoter that is located close to the early non-T-A-T-A box promoter and is used both in vivo and in vitro. (Author abstract) (28 Refs)

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2. GLUCOCORTICOID REGULATION OF THE HA-MUSV P21 GENE CONFERRED BY SEQUENCES FROM MOUSE MAMMARY TUMOR VIRUS.

Huang AL, Ostrowski MC, Berard D, Hager GL
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Cell; 27(2):245-255 1981

Molecular chimeras with the p21 transforming gene of Harvey murine sarcoma virus linked to DNA containing the long terminal repeat (LTR) of mouse mammary tumor virus (MMTV) have been constructed. Transformants of NIH 3T3 cells induced by transfection with MMTV LTR-p21 hybrid DNA have been identified that express the normal p21 gene product. The levels of p21 RNA and protein in these transformants are regulated by physiological concentrations of dexamethasone, a synthetic glucocorticoid hormone. Hybrid transcripts containing p21 gene sequences originate at the normal MMTV viral initiation site. It is concluded that sequences necessary for hormonal control of transcription are completely specified by the viral genome and probably map within the viral LTR. (Author abstract) (45 Refs)

3. NUCLEOLAR SILVER STAINED GRANULES IN RAT YOSHIDA SARCOMA CELLS AFTER RNA SYNTHESIS INHIBITION.

Kacerovska H, Likovsky Z, Smetana K
(c/o Smetana) Inst. Experimental Medicine, Czechoslovak Acad. Sciences, 128 00 Praha 2, Albertov 4, Czechoslovakia
Neoplasma; 28(5):513-516 1981

The number of nucleolar silver stained granules representing nucleolus organizer regions in interphase nuclei was studied in Yoshida ascitic sarcoma cells without and after the inhibition of the nucleolar RNA synthesis with actinomycin D or cyclophosphamide. The results demonstrated that the number of nucleolar silver stained granules decreased after the inhibition of the nucleolar RNA synthesis with these drugs disregarding the mode of their action. In addition, the decrease of nucleolar silver stained granules in number produced by actinomycin D was dose dependent. Similarly, the number of nucleoli without silver stained granules increased depending on the dose of the administered actinomycin D. (Author abstract) (13 Refs)

4. A MODEL OF SENESCENCE AS THE PIECEWISE LOSS OF CONTROL OVER TRANSCRIPTION.

Jablonka E, Jablonka P
1155 East Waverly, Tucson, AZ, 85719
Med Hypotheses; 7(12):1401-1413 1981

The hypothesis that senescence is an accumulating loss of control over transcription of DNA into heterogeneous nuclear RNA (hnRNA), particularly hnRNA associated with cell differentiation, is described. Both masking errors and error-prone repair mechanisms are proposed to be involved in senescence. Given that DNA transcription of DNA into hnRNA is controlled for each species of hnRNA by an on-off switch at the beginning of each hnRNA template, then control over transcription may be independently lost over each control site. If an incorrect switch setting is conserved during replication and mitosis after the pattern of conservation of DNA-binding molecules and DNA bound histones, then the errors are heritable and can accumulate from one cell generation to the next. This theory of senescence can be used to derive the Hayflick limit for cultured cells and explains the link between aging and cancer. (19 Refs)

5. ALTERATIONS IN RIBONUCLEIC ACID SYNTHESIS BY CHROMIUM (III).

Okada S, Ohba H, Taniyama M
Dept. Environmental Biochemistry, Shizuoka Coll. Pharmacy, 2-2-1 Oshika, Shizuoka-shi 422, Japan
J Inorg Biochem; 15(3):223-231 1981

The effects of Cr(III) on DNA- and chromatin-directed male ddY mouse liver RNA synthesis were studied, and compared with the effects of Al(III), Cu(II), Zn(II), Cd(II), Hg(II), Be(II), and Pb(II). Assay for RNA synthesis was by liquid scintillation spectrometric measurement of (5-3H) uridine monophosphate incorporation. Incubation of metal, DNA, Escherichia coli RNA polymerase, and RNA precursors inhibited RNA synthesis 15-50% compared to metal-less control. However, when metals were incubated with the DNA for 5 min prior to addition of the remainder of the mixture, Cr(III) was associated with significant stimulation of synthesis, whereas the other metals inhibited synthesis. Similar results were obtained when RNA synthesis was directed by chromatin. Preincubation of RNA polymerase with Cr(III) caused marked inhibition of RNA synthesis in both DNA- and chromatin-directed systems, but preincubation of DNA or chromatin with Cr(III) gave significant stimulation, suggesting that binding of Cr(III) to RNA polymerase reduced enzyme activity, but that binding of DNA or chromatin enhanced their template activities. Cr(III) presence stimulated Mg++-activated RNA synthesis by endogenous RNA polymerases in isolated mouse liver nuclei, but did not stimulate Mn++-(NH4)2SO4-activated synthesis; most other metals inhibited RNA synthesis in nuclei, and none stimulated it. (20 Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

6. T ANTIGEN REPRESSION OF SV40 EARLY TRANSCRIPTION FROM TWO PROMOTERS.

Hansen U, Tenen DG, Livingston DM, Sharp PA
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 27(3):603-612 1981

The SV40 early mRNAs encode large (T) and small (t) tumor antigens. During the lytic cycle, the 5' termini of the early mRNAs undergo a shift: shortly after infection only an initiation site downstream from the TATA box is utilized; later an upstream initiation site becomes prominent. Both initiation sites are utilized in an in vitro transcription extract. D2T, a T antigen analog, specifically represses transcription in vitro from both initiation sites, but at different concentrations. Binding of D2T to Site I suppresses initiation from the site downstream of the TATA box; binding to Sites II and I suppresses initiation from the upstream site. The role of T antigen binding in repression of transcription and in the shift of initiation sites on the early strand is discussed. (Author abstract) (52 Refs)

7. LATE MESSENGER RNA PRODUCTION BY VIABLE SIMIAN VIRUS 40 MUTANTS WITH DELETIONS IN THE LEADER REGION.

Piatak M, Subramanian KN, Roy P, Weissman SM
Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Mol Biol; 153(3):589-618 1981

We have analyzed the structure of simian virus 40 messenger RNA in cells infected with mutant viruses in which DNA encoding various segments of the late leader has been deleted. The results show that large amounts of stable unspliced mRNA may accumulate in the cytoplasm and that some unspliced RNA appears in polyribosomes. The locations of the prominent 5' ends of mRNA are influenced by relatively remote downstream sequences and bear no fixed relationship to any sequence of the simian virus 40 DNA retained in the mutant virus. Sequences downstream from the leader template may play a role in determining the region in which transcription initiates preferentially. Splices may occur even when nucleotides further than seven residues downstream from the upstream end of the splice are altered, and alternative splices with one junction in common may be differently affected by deletions near the common splice junction. (Author abstract) (64 Refs)

8. MECHANISM OF INTERFERON ACTIVITY. STABILITY AND TRANSLATION OF SIMIAN VIRUS-40 EARLY MRNA CODING FOR T-ANTIGEN IS COMPARABLE IN UNTREATED AND INTERFERON-TREATED MONKEY CELLS.

Daher KA, Samuel CE
Section Biochemistry and Molecular Biology, Dept. Biological Sciences, Univ. California, Santa Barbara, CA, 93106
Biochem Biophys Res Commun; 101(2):697-703 1981

Effects of interferon (IF)-treatment on the translation and functional stability of Simian virus 40 (SV40) early messenger (m)RNA coding for T-antigen under conditions where SV40 early RNA synthesis is apparently unaffected by IF were investigated. African green monkey kidney cells were infected with a tsA mutant of SV40 at an elevated temperature (40 C). The rate of T-antigen synthesis in tsA-infected cells at varying times following the addition of 1 ug/ml actinomycin D to the medium 36 hr post infection was determined to decide whether the stability of SV40 early mRNA differed between untreated and IF-treated cells. The SV40 mRNA coding for T-antigen had a half-life of about 3 hr, and there was no significant difference between the IF-treated and untreated cells. The fact that the decay of SV40 early RNA is indistinguishable between the IF-treated and untreated cells was thought to augment other facts and indicate that an enhanced degradation of SV40 early RNA by an IF-mediated RNAase probably does not play a major role in the antiviral action of IF in SV40 lytic infections. (25 Refs)

9. EXPRESSION OF ERYTHROID DIFFERENTIATION AND TERMINAL CELL DIVISION IN INDUCED FRIEND LEUKEMIA CELLS.

Gambari R, Marks PA, Rifkind RA, Farace M, Fantoni A
Istituto di Biologia Generale, Universita di Roma, Roma, Italy
Acta Biol Med Ger; 40(4/5):511-518 1981

The relationship between cell cycle and globin gene expression was investigated during late differentiation of Friend leukemia cells (FLC) treated with hemin. Cell growth and cell cycle kinetics in the FLC line DS19 were determined by propidium iodide staining and by flow microfluorometry analysis of relative DNA content. Globin gene expression was studied by molecular hybridization of phenol extracted cytoplasmic RNA with mouse globin (3H)-complementary (c)DNA or by cDNA cellulose chromatography of pulse-labeled (3H)RNA purified from the nuclei or cytoplasm of FLC cultured with the inducer hexamethylenebisacetamide (HMBA) or hemin. In FLC treated with HMBA, accumulation and translation of globin messenger (m)RNA and Hb were associated with terminal cell division. Since hemin did not induce expression of genes responsible for terminal cell division, the relationship between cell cycle and globin gene expression was determined during late differentiation of FLC treated with hemin. Results demonstrate that terminal cell division does not necessarily occur in cells which accumulate both globin mRNA and Hb, suggesting that these features are not necessarily coupled in leukemia erythroid differentiation. (14 Refs)

10. SEQUENCE COMPLEXITY AND DIVERSITY OF POLYADENYLATED RNA MOLECULES OF HUMAN NORMAL RESTING, PHA-STIMULATED AND LEUKEMIC LYMPHOCYTES.

Torelli G, Ferrari S, Donelli A, Cadossi R, Ferrari S, Bosi P, Torelli U
Center for Experimental Hematology, Univ. Modena, 41100 Modena, Italy
Nucleic Acids Res; 9(24):7013-7032 1981

The abundance and complexity of total poly(A)+ RNA of human normal unstimulated lymphocytes, PHA-stimulated and leukemic lymphocytes were examined using the cDNA-poly(A)+ RNA hybridization technique. It was found that in both PHA-stimulated and leukemic lymphocytes the complexity of total poly(A)+RNA is strongly reduced in respect to normal unstimulated lymphocytes. The difference is due to a small portion, by wt, of high complexity sequences, suggesting the involvement of nuclear, not necessarily transcriptional, events. Moreover the heterologous hybridizations show that: (1) in PHA-stimulated lymphocytes there is a set of highly abundant sequences which are represented in normal and leukemic lymphocytes at a very reduced rate; (2) the sequences abundant in normal unstimulated lymphocytes are less represented in leukemic lymphocytes; the converse also is true, but at a lower extent. On the basis of available data, it is suggested that the observed changes in the abundance pattern of PHA-stimulated lymphocytes may be related mainly to a difference in the half-life of the mRNAs, while those of leukemic lymphocytes require some transcriptional or post-transcriptional nuclear event. (Author abstract) (47 Refs)

11. SELECTIVE INHIBITION BY SODIUM BUTYRATE OF GLUCOCORTICOID-INDUCED TYROSINE AMINOTRANSFERASE SYNTHESIS IN HEPATOMA TISSUE-CULTURED CELLS.

Tichonicky L, Santana-Calderon MA, Defer N, Giesen EM, Beck G, Kruh J
Institut de Pathologie et Biologie Cellulaire et Moleculaire, Centre Hospitalier Universitaire Cochin-Port Royal, 24 Rue du Faubourg-Saint-Jacques, F-75014 Paris, France
Eur J Biochem; 120(3):427-433 1981

Sodium butyrate at a 5 mM concentration prevents the induction of tyrosine aminotransferase in hepatoma culture cells, without affecting the basal level of the enzyme. This effect is reversible immediately after the removal of butyrate, or after a lag, if butyrate was present for more than 2 hr. Neither the amount of cellular RNA nor the rate of total RNA synthesis were affected by sodium butyrate. Furthermore butyrate does not inhibit protein synthesis: [35S]methionine incorporation into proteins, measured in a reticulocyte lysate system, shows no significant difference between the translation capacity of the RNAs from butyrate-treated cells and from dexamethasone-induced or uninduced cells. Nevertheless, when tyrosine aminotransferase was isolated from the translation products by its specific antiserum and analyzed by gel electrophoresis, we observed that the amount of the enzyme synthesized in the presence of RNAs from dexamethasone/butyrate-treated cells was strongly diminished relative to that synthesized in the presence of RNA from dexamethasone-induced cells. These experiments indicate that the treatment of the cells with butyrate decreases the activity of the specific messenger RNA for tyrosine aminotransferase to a level close to the basal level. Butyrate does not prevent the penetration of the hormone and has a limited effect on the translocation of the glucocorticoid-receptor complex to the nucleus. We therefore conclude that the effect of sodium butyrate might be inherent either to an impairment of an early step of the hormone-chromatin interaction or to an alteration of the transcription process of some specific genes. The rapidity and the complete reversibility of the effects of butyrate suggest that it does not irreversibly alter the structures which are the targets of its action. (Author abstract) (51 Refs)

12. EXPRESSION OF THE ALBUMIN GENE IN RAT HEPATOMA CELLS AND THEIR DEDIFFERENTIATED VARIANTS.

Cassio D, Weiss MC, Ott MO, Sala-Trepat JM, Fries J, Erdos T
Centre de Genetique Moleculaire, Centre National de la Recherche Scientifique, 91190 Gif-sur-Yvette, France
Cell; 27(2):351-358 1981

Rat hepatoma clones whose cells do and do not produce albumin, as well as somatic hybrids between the two types of cells, have been examined for albumin mRNA. A direct proportionality between the rate of albumin production and the concentration of albumin mRNA sequences was found for all albumin-producing hepatoma and hybrid clones, indicating that rate of synthesis of the protein is determined by the concentration of its mRNA. Albumin-negative dedifferentiated variant and somatic hybrid cells contain fewer than one to five molecules of albumin mRNA per cell; the block in expression of the gene appears to be at the same (probably transcriptional) level in variants and their somatic hybrids. (Author abstract) (50 Refs)

13. ORGANIZATION AND EXPRESSION OF ENDOGENOUS VIRUS-LIKE (VL30) DNA SEQUENCES IN NONTRANSFORMED AND CHEMICALLY TRANSFORMED MOUSE EMBRYO CELLS IN CULTURE.

Courtney MG, Schmidt LJ, Getz MJ
(c/o Getz) Dept. Cell Biology, Mayo Clinic/Foundation, Rochester, MN, 55905
Cancer Res; 42(2):569-576 1982

A cloned mouse DNA fragment containing an endogenous 'virus-like' DNA (VL30 DNA) sequence was identified by virtue of its ability to hybridize to the virus-like RNA component of mixed-pseudotype AKR-murine leukemia virus virions, its lack of detectable sequence homology with cloned AKR-murine leukemia virus DNA, and its hybridization to a 5.6 kilobase pair (30S) cellular polyadenylic acid [poly(A)]-containing RNA species. Restriction enzyme mapping of the cloned mouse fragment revealed the presence of a 5-to 6-kilobase pair VL30 DNA segment flanked by non-VL30 segments of approx 7 and 0.3 kilobase pairs. Southern blot analysis of VL30 DNA sequence organization in the DNA of two nontransformed mouse cell lines (AKR-2B, C3H/10T1/2) and two chemically transformed derivatives (AKR-MCA, C3H/MCA-58) revealed 15 to 20 bands organized in an apparent strain-specific pattern. Within a given strain, however, no differences were detectable between the nontransformed cells and their chemically transformed counterparts. The expression of VL30 genes in the above cell lines was assayed by hybridization of 32P-labeled poly(A)-containing polysomal RNA to several internal restriction fragments derived from the cloned VL30 DNA sequence. The level of VL30 RNA was enhanced approx 10-fold in both chemically transformed cell lines as compared to the nontransformed cell lines (under normal growth conditions). In addition, nontransformed AKR-2B cells maintained in the presence of purified epidermal growth factor exhibited similarly enhanced levels of VL30 RNA sequences in polysomal RNA. Since these cells display several growth characteristics of transformed cells but, in an epidermal growth factor-dependent and completely reversible fashion, these data suggest that the expression of VL30 ge nes is not simply incidental to chemically transformed cells but may be related to alterations in growth control. (Author abstract) (34 Refs)

14. THE LEADER SEQUENCE OF THE SUBGENOMIC MRNA'S OF ROUS SARCOMA VIRUS IS APPROXIMATELY 390 NUCLEOTIDES.

Hackett PB, Swanstrom R, Varmus HE, Bishop JM
Dept. Genetics and Cell Biology, Univ. Minnesota, St. Paul, MN, 55108
J Virol; 41(2):527-534 1982

The subgenomic mRNA's of Rous sarcoma virus share a common 5' leader sequence spliced from genomic RNA. We have examined the 5' terminal sequences of four Rous sarcoma virus RNAs: virion RNA and three species of intracellular mRNA which direct the synthesis of the RSV gene products. The lengths of the leaders on the RNAs were determined by the extent that they could protect cloned Rous sarcoma virus DNA fragments from S1 nuclease digestion after RNA-DNA hybridization. We found that the subgenomic mRNA's that direct the synthesis of the env and src gene products have uninterrupted spliced leader sequences, of approx 390 nucleotides, whereas virion RNA and full-length intracellular viral RNA have 5' termini homologous to the cloned viral DNA probe over at least the first 735 bases. In the accompanying manuscript we have determined the nucleotide sequence of the 5' end of the Rous sarcoma virus genome, including the candidate splice donor site identified here. (Author abstract) (46 Refs)

15. TRANSFORMATION-DEFECTIVE MUTANT OF ADENOVIRUS TYPE 5 CONTAINING A SINGLE ALTERED E1A MRNA SPECIES.

Carlock LR, Jones NC
Dept. Biological Sciences, Purdue Univ., West Lafayette, IN, 47907
J Virol; 40(3):657-664 1981

A mutant of adenovirus type 5 containing an octanucleotide insert in region E1a of the viral genome was constructed. The insert was present in only one (13s) of the three overlapping mRNA's synthesized from this region. The insert was within the sequences removed by RNA splicing during the production of the other two mRNA's. The insertion resulted in a shift in the translational reading frame of the 13s mRNA and the probable premature termination of translation. The mutant was defective for viral DNA replication in HeLa cells and the transformation of rat embryo and baby rat kidney cells, indicating that a product encoded by the 13s mRNA is required for these two processes. Other early regions of the genome were expressed in HeLa cells infected by this mutant although in some cases the expression was decreased as compared with wild-type-infected cells. (Author abstract) (27 Refs)

16. TRYPTIC AND CHYMOTRYPTIC METHIONINE PEPTIDE ANALYSIS OF THE IN VITRO TRANSLATION PRODUCTS SPECIFIED BY THE TRANSFORMING REGION OF ADENOVIRUS TYPE 2.

Halbert DN, Raskas HJ
Dept. Microbiology, Health Sciences Center, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Virology; 116(2):406-418 1982

Early region 1 (E1) cytoplasmic RNAs of adenovirus Type 2 were translated in vitro. Structural relationships between these proteins were then established by tryptic and chymotryptic digestion and two-dimensional peptide mapping. This analysis also allowed a direct comparison of these proteins with polypeptides isolated from early infected cell extracts and previously assigned to E1 by indirect means. E1a (0-4.5%) RNA encodes five proteins in vitro: 35K, 41K, 47K and 53K at early times, and a 28K protein at later times in infection. These five proteins are all highly related by peptide mapping analysis, and are also related to a group of four proteins isolated from cell extracts prepared early in infection. E1b (4.5-11.0%) early RNA encodes 52K and one or more 15K proteins in vitro. The 52K protein shares tryptic peptides with a 53K immunoprecipitated T antigen. A 15K protein shares some peptides with the 52K protein and with several proteins isolated from infected cells. At intermediate to late times, E1b RNA encodes a 12K protein that corresponds to the virion structural polypeptide IX. These data also permit the correlation of E1 proteins synthesized in vitro with the polypeptides predicted by E1 sequence analysis. (Author abstract) (45 Refs)

17. PHOSPHORYLATION OF RIBOSOMAL PROTEIN S6: RELATIONSHIP TO PROTEIN SYNTHESIS IN HELA CELLS.

Nielsen PJ, Duncan R, McConkey EH
Friedrich-Miescher-Institut, Postfach 273, CH-4002 Basel, Switzerland
Eur J Biochem; 120(3):523-527 1981

The time of S6 phosphorylation and several aspects of protein synthesis have been studied in suspension cultures of HeLa cells, following transfer to fresh medium and serum. The phosphorylation of S6 is not temporally correlated with changes in polypeptide initiation and elongation rates, as judged from polysome profiles. Phosphorylation of S6 can be maximal within 30 min after transfer; elongation and initiation rates increase coordinately and more slowly, becoming maximal about 6 hr after transfer, a time at which the net phosphorylation of protein S6 is greatly reduced or negligible. Recruitment of messenger RNA into polysomes is another response to fresh medium and serum; this response occurs almost as rapidly as the phosphorylation of S6. We suggest that the phosphorylation of S6 may play a role in messenger RNA recruitment. (Author abstract) (20 Refs)

18. CELLULAR GENES ANALOGOUS TO RETROVIRAL ONC GENES ARE TRANSCRIBED IN HUMAN TUMOUR CELLS.

Eva A, Robbins KC, Andersen PR, Srinivasan A, Tronick SR, Reddy P, Ellmore NW, Galen AT, Lautenberger JA, Papas TS, Westin EH, Wong-Staal F, Gallo RC, Aaronson SA
Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Nature; 295(5845):116-119 1982

Polyadenylated RNAs of certain human tumor cell lines are shown to contain trans cripts related to the cell-derived transforming onc genes of molecularly cloned primate, murine or avian transforming retrovirus genomes. Thus, analogues of retroviral transforming genes are both present and frequently expressed in human neoplastic cells. (Author abstract) (52 Refs)

19. ANALYSIS OF INTERFERON MRNA IN HUMAN FIBROBLAST CELLS INDUCED TO PRODUCE INTERFERON.

Raj NB, Pitha PM
Oncology Center, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Proc Natl Acad Sci USA; 78(12):7426-7430 1981

The levels of interferon mRNA as a function of interferon induction by poly(rI)-poly(rC) in human fibroblast cells were determined by RNA hybridization using a cloned beta interferon cDNA and by translation in Xenopus oocytes. Whereas previous studies analyzed mixtures of interferons, the availability of the cloned beta interferon cDNA and the antiserum to purified beta interferon enabled us to focus on the expression of only one class (beta) of interferon genes. The induction of interferon synthesis depends primarily on the accumulation of interferon beta mRNA in the cells, and the interferon beta mRNA rapidly disappears several hours after its appearance in the cytoplasm. No detectable interferon beta mRNA sequences are present in uninduced cells. The degradation of interferon beta mRNA in the induced cells requires ongoing protein synthesis; accumulation of interferon beta mRNA was observed in the continuous presence of cycloheximide. The interferon beta mRNA detected at the early stages of induction is 1,100 nucleotides long and its size progressively decreases with time. By both the hybridization and the translational assay in Xenopus oocytes, only one size of interferon beta mRNA and one species of beta interferon could be identified. (Author abstract) (33 Refs)

20. MOLECULAR BASIS FOR INCREASED SYNTHESIS OF ALBUMIN IN RAT LIVER AFTER THIOACETAMIDE ADMINISTRATION.

Chakrabartty PK, Chattopadhyay S K, Schneider WC
(c/o Chattopadhyay), NIH, Building 41, Room A-114, Bethesda, MD, 20205
Cancer Res; 42(2):421-428 1982

Administration of thioacetamide to rats for 4 days has been shown previously to increase the activity of liver messenger RNA (mRNA) and to disproportionately increase the activity of albumin mRNA in the wheat germ translation system. We have explored the possibility that administration of thioacetamide quantitatively alters the transcription of rat liver unique DNA. Nucleic acid hybridization between radioactive rat liver unique DNA and RNA from untreated as well as 4-day thioacetamide-treated rat liver indicates that that normal extent of transcription is not altered by the drug treatment. We also investigated the possibility that thioacetamide treatment increases the level of mRNA in general or of albumin mRNA in particular. Albumin mRNA, which is the most abundantly represented population in rat liver cytoplasm ic mRNA, was further enriched by sucrose gradient fractionation of the liver mRNA. Synthesis of complementary DNA (cDNA) and then use of the strategy of limited hybridization yielded the cDNA corresponding to albumin mRNA. Hybridization of the fractionated cDNA with mRNA from untreated livers as well as from livers with increasing days of treatment shows no change in the level of albumin mRNA. The results indicate that drug treatment induces the augmented synthesis of albumin by disproportionately increasing the translational activity of albumin mRNA. Quantitation of gene dosage by comparison of hybridization kinetics of fractionated cDNA and unique [3H]DNA with total rat cellular DNA indicates that there are not more than two copies of the albumin gene present in the rat genome. (Author abstract) (23 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

21. RNA POLYMERASE II IN C6 GLIOMA CELLS. ALPHA-AMANITIN BLOCKADE OF CAMP PHOSPHODIESTERASE INDUCTION BY BETA-ADRENERGIC STIMULATION.

Schwartz JP
Lab. Preclinical Pharmacology, Natl. Inst. Mental Health, Saint Elizabeth's Hosp., Washington, DC, 20032
Exp Cell Res; 137(1):39-45 1982

C6 glioma cells contain an RNA polymerase activity which is nuclear, requires Mn++ and high ionic strength for maximal activity, is inhibited by low concentrations of alpha-amanitin, or by actinomycin D, and is therefore classified as RNA polymerase II. Exposure of intact cells to isoproterenol, a beta-adrenergic receptor agonist, results in an increase in the activity of cAMP phosphodiesterase. This increase in phosphodiesterase activity is blocked by incubation of the cells with alpha-amanitin or actinomycin D, suggesting that RNA polymerase II is necessary for synthesis of mRNA for the increase in phosphodiesterase activity. RNA polymerase II activity is not increased in isoproterenol-treated cells, although it is more strongly inhibited by alpha-amanitin. The Ki for the effect of alpha-amanitin on intact cells is 250 nM, and the inhibitor acts rapidly, with a maximal effect within 15 min of exposure. The effect of alpha-amanitin is very specific, as no change in various cytoplasmic or nuclear enzymes or metabolites was observed. (Author abstract) (21 Refs)

22. FURTHER CHARACTERIZATION OF THE EFFECTS OF 3-METHYLCHOLANTHRENE ADMINISTRATION UPON HEPATIC RIBONUCLEIC ACID POLYMERASE ACTIVITIES.

Liberator PA, Bresnick E
(c/o Bresnick) Vermont Regional Cancer Center, Univ. Vermont Coll. Medicine, Burlington, VT, 05405
Chem Biol Interact; 38(1):53-73 1981

The administration of 3-methylcholanthrene (MC) to rats results in a marked increase in the specific activities of hepatic RNA polymerases I and II. In the present study, we were able to show that this increase was not caused by a shift in the ratio of 'free' to 'template-engaged' RNA polymerase. By means of binding studies with [3H]amatoxin, we were unable to demonstrate any increase in the number of RNA polymerase II molecules in liver after MC administration to the rats. RNA polymerase I was purified in excess of 3,000-fold from hepatic nuclei isolated both from control and MC-treated rats. The stimulation in activity was demonstrated at each step in the purification scheme until glycerol sedimentation analysis. Results from cation-exchange chromatography on phosphocellulose indicated that the polycyclic hydrocarbon increased the enzyme activity of RNA polymerase Ib somewhat specifically. Subsequent to glycerol gradient centrifugation, this stimulatory advantage was no longer evident. Reconstitution experiments revealed the presence of a stimulatory component, which was demonstrated in low mol wt fractions from both control and experimental preparations. (Author abstract) (47 Refs)

OTHER RELATED STUDIES

23. ANTI-TUMOR EFFECT OF SYNGENEIC SPLEEN CELLS TREATED WITH IMMUNE RNA AND TUMOR ANTIGEN.

Fukushima M, Colmerauer ME, Nayak SK, Koziol JA, Pilch YH
(c/o Pilch), Univ. Hosp.-H891B, 225 Dickinson St., San Diego, CA, 92103
Int J Cancer; 29(1):113-117 1982

The antitumor effect of syngeneic spleen cells, xenogeneic immune RNA (I-RNA) and tumor antigen (TA) was studied in a chemically induced (N-methyl-N-nitrosourethane) colon carcinoma model in BALB/c mice. When the mice were treated, sequentially, with these three elements by local injection under the tumor, complete tumor regression was observed in 25% of the animals. Complete tumor regression was observed in 17% of animals treated by injection of spleen cells pre-incubated with I-RNA in vitro followed by an injection of TA. When spleen cells were treated first with I-RNA and then with mitomycin-C, therapeutic benefit was obtained and the survival rate of mice treated with these spleen cells and TA was significantly higher than that of the control group (no treatment). The antitumor effect of this treatment was abrogated completely when spleen cells were treated with mitomycin-C prior to I-RNA incubation. When spleen cells were incubated with TA in vitro or after incubation with I-RNA and then injected into tumor-bearing mice, no antitumor effect was noted. These data suggest that DNA synthesis and/or lymphocyte proliferation is essential for the action of I-RNA in sensitizing lymphocytes but not essential in the interaction of I-RNA-sensitized lymphocytes with TA. In addition it appeared that, under the conditions used, the participation of host factors was essential in the latter interaction, since treatment of I-RNA-sensitized lymphocytes with TA in vitro was ineffective. (Author abstract) (13 Refs)

24. IMMUNOTHERAPY OF A MURINE COLON CANCER WITH SYNGENEIC SPLEEN CELLS, IMMUNE RNA AND TUMOR ANTIGEN.

Fukushima M, Colmerauer ME, Nayak SK, Koziol JA, Pilch YH
1st Dept. Surgery, Hirosaki Univ. Sch. Medicine, Hirosaki, Japan
Int J Cancer; 29(1):107-112 1982

In combination with xenogeneic immune RNA (I-RNA) and tumor antigen (TA), syngeneic spleen cells inhibited the growth of a N-methyl-N-nitrosourethane-induced colon carcinoma (CT-26) in BALB/c mice. The sequential administration of 1 x 10(7) spleen cells, 1 mg of anti-CT-26 I-RNA and 0.4 mg of CT-26 TA resulted in a 20% survival rate of mice bearing established CT-26 tumors. On the other hand, administration of the spleen cells only, I-RNA only or TA only was not effective in inhibiting tumor growth. Similarly, when any one of the three agents (I-RNA, TA and spleen cells) was omitted, no anti-tumor effect was obtained. A higher dose (1 x 10(8)) and a lower dose (1 x 10(6)) of spleen cells decreased the antitumor effect of this combination therapy. A higher dose (2 mg) and a lower dose (0.5 mg) of I-RNA, as well as a higher dose of TA (0.8 mg) had no influence on the antitumor effect. However, a lower dose of TA (0.2 mg) in combination with spleen cells and I-RNA decreased the antitumor effect. When all three agents were administered at higher or lower doses, no antitumor effect was obtained. When mice bearing CT-26 tumors were treated with spleen cells, plus I-RNA directed against a syngeneic but antigenically different tumor (BP/B/5) and BP/B/5 TA, with spleen cells plus CT-26 I-RNA and BP/B/5 TA, or with spleen cells plus BP/B/5 I-RNA and CT-26 TA, no antitumor effect was observed. These results indicate that the antitumor responses observed were due to tumor-specific immune responses. In conclusion, in order to obtain growth retardation or regression of established CT-26 tumor transplants, the sequential administration of all three agents (spleen cells, I-RNA and TA) was required. The optimal doses of each agent were found to be 1 x 10(7) spleen cells, 0.5 mg or 1 mg of I-RNA and 0.4 mg of tumor antigen. Higher or lower doses decreased the antitumor effect. Tumor-specific immune reactions appeared to be involved. (Author abstract) (21 Refs)

25. STRUCTURE OF RETROVIRAL RNAS PRODUCED BY CELL LINES DERIVED FROM SPONTANEOUS LYMPHOMAS OF AKR MICE.

Pedersen FS, Crowther RL, Hays EF, Nowinski RC, Haseltine WA
Dept. Molecular Biology, Univ. Aarhus, DK-8000 Aarhus C, Denmark
J Virol; 41(1):18-29 1982

The retrovirus expression of eight independent lymphoid cell lines derived from spontaneous thymomas of AKR mice was investigated. The RNase T1 finger-prints of viral 70S RNA produced by these cell lines were compared with genome structures of the non-leukemogenic Akv virus and with two types of cloned leukemogenic viruses derived from one of the thymoma cell lines. Viral RNAs from three cell lines, SL3, 4, and 7, were indistinguishable from one another. The fingerprint patterns indicated that these cell lines produce equal amounts of two prototype, leukemogenic SL viruses that were previously isolated from the SL3 cell line. Viral RNA produced by the SL1 and SL2 cell lines contained similar components, but at a different ratio. Two other cell lines (SL5 and SL11) produced viral RNAs that resemble those of AKR mink cell focus-forming viruses. One additional line, SL9, produced viral RNA of a novel structure. The complex pattern of viral RNA expression observed for these lymphoid cell lines can be interpreted in terms of recombination among three types of endogenous viral sequences: the Akv virus, a xenotropic virus, and an SL (for spontaneous leukemia) virus. (Author abstract) (25 Refs)

26. ASSOCIATION OF 3' TERMINAL RNA SEQUENCES WITH AVIAN LEUKOSIS VIRUSES CAUSING A HIGH INCIDENCE OF OSTEOPETROSIS.

Schmidt EV, Kenne JD, Linial M, Smith RE
(c/o Smith) Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
Virology; 116(1):163-180 1982

The T1 ribonuclease fingerprints of the genomic RNAs of four osteopetrosis-inducing, avian leukosis viruses were compared with fingerprints of the RNAs from four unrelated avian retroviruses. Two oligonucleotides at the 3' end of the genomes of all osteopetrosis-inducing viruses were not present in the RNAs of the four viruses that did not induce osteopetrosis. This evidence suggests that genetic information related to the induction of a high frequency of osteopetrosis is present at the 3' end of the genomes of these viruses. (Author abstract) (41 Refs)

27. COMPARATIVE RESTRICTION ENDONUCLEASE MAPS OF PROVIRAL DNA OF THE PRIMATE TYPE C SIMIAN SARCOMA-ASSOCIATED VIRUS AND GIBBON APE LEUKEMIA VIRUS GROUP.

Trainor CD, Wong-Staal F, Reitz MS
(c/o Reitz) Div. Cancer Treatment, Lab. Tumor Cell Biology, NCI, Bethesda, MD, 20205
J Virol; 41(1):298-308 1982

Extrachromosomal DNA was purified from canine thymus cells acutely infected with different strains of infectious primate type C viruses of the woolly monkey (simian) sarcoma helper virus and gibbon ape leukemia virus group. All DNA preparations contained linear proviral molecules of 9.1 to 9.2 kilobases, at least some of which represent complete infectious proviral DNA. Cells infected with a replication-defective fibroblast-transforming sarcoma virus and its helper, a replication-competent nontransforming helper virus, also contained a 6.6-to 6.7-kilobase DNA. These proviral DNA molecules were digested with different restriction endonucleases, and the resultant fragments were oriented to the viral RNA by a combination of partial digestions, codigestion with more than one endonuclease, digestion of integrated proviral DNA, and hybridization with 3'-and 5'-specific viral probes. The 3'- and 5'-specific probes each hybridized to fragments from both ends of proviral DNA, indicating that, in common with those of other retroviruses, these proviruses contain a large terminal redundancy at both ends, each of which consists of sequences derived from both the 3' and 5' regions of the viral RNA. The proviral sequences are organized 3',5'-unique-3',5'. Four restriction enzymes (KpnI, SmaI, PstI, and SstI) recognized sites within the large terminal redundancies, and these sites were conserved within all the isolates tested. This suggests that both the 3' and 5' ends of the genomic RNA of these viruses are extremely closely related. In contrast, the restriction sites within the unique portion of the provirus were not strongly conserved within this group of viruses, even though they were related along most of their genomes. Whereas the 5' 60 to 70% of the RNA of these viruses was more closely related by liquid hybridization experiments than was the 3' 30 to 40%, restriction sites within this region were not preferentially conserved, suggesting that small sequence differences or point mutations or both exist throughout the entire unique portion of the genome among these viruses. (Author abstract) (37 Refs)

28. A REVIEW OF APPROACHES TO VIRAL CHEMOTHERAPY.

Gordon M, Buchanan RL, Crenshaw RR, Kerridge KA, MacNintch JE, Siminoff P

Bristol Lab., Syracuse, NY, 13201

J Med; 12(5):289-384 1981

Progress in the field of viral chemotherapy is reviewed. The following topics were discussed: impact of viral diseases; viral morphology, physiology, replication, and pathogenicity; viral biochemistry; synthetic antiviral agents; recent developments in interferon research; immune stimulants, and future prospects. Role of viruses in oncogenesis is illustrated by the transmission of avian leukemia and Rous sarcoma. Other viruses involved in leukemia, sarcoma, and carcinoma were isolated from primates, cows, hamsters, horses, rats, and cats. DNA-containing oncogenic viruses include papovaviruses, adenoviruses, herpesviruses, and poxviruses; RNA-containing tumor-inducing viruses include the avian leukemia-sarcoma complex, the murine leukemia-sarcoma complex, and the primate oncornaviruses. Neoplastic cell transformation after virus infection can be characterized by by changes in cell appearance, increase in cellular metabolism, increase in multiplication rate, and loss of contact inhibition. (370 Refs)

29. REGULATION OF SV40 GENE EXPRESSION.

Graessmann A, Graessmann M, Mueller C
Institut fur Molekularbiologie und Biochemie, Freien Universitat Berlin, Berlin, W. Germany
Adv Cancer Res; 35:111-149 1981

The microinjection approach to the study of simian virus 40 (SV40) and polyoma virus (PV) gene expression is discussed. The technique permits placing of biological material from virtually any source directly into living, single-tissue culture cells using glass micropipettes. Cell type dependence of SV40 and PV gene expression is presented in relation to permissive, nonpermissive, semi-permissive, and virus-resistant cells. Functions of SV40 tumor antigens are considered, including induction of cellular and viral DNA systems, regulation of late and early SV40 gene expression, stimulation of rRNA synthesis, helper function for adenovirus and U antigenicity, and reduction of the actin cable structure. Experiments with microinjection of SV40 DNA fragments to induce cellular transformation and applications of microinjection are reviewed. (78 Refs)

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RNA TRANSCRIPTION/ SYNTHESIS

1. INDUCER-RESPONSIVE EXPRESSION OF THE CLONED HUMAN INTERFERON BETA1 GENE INTRODUCED INTO CULTURED MOUSE CELLS.

Ohno S, Taniguchi T
Dept. Biochemistry, Cancer Inst., Japanese Foundation Cancer Res., Tokyo 170, Japan
Nucleic Acids Res; 10(3):967-977 1982

A hybrid plasmid was constructed from pSV2-Egogpt and the cloned 1.8 kilobase chromosomal DNA segment which contains the human interferon (HIFN-beta1) gene and its flank-

HE 20. 3173/

ing sequences. Cultured mouse FM3A cells were transfected by the hybrid plasmid and several Ecogpt+ clones were selected. Southern blot analysis of the DNA from these mouse cell clones showed that two of them contained a few copies of the 1.8 kilobase human DNA. Synthesis of mRNA characteristic of the HIFN-beta1 mRNA increased as measured by RNA blot analysis when those clones were treated with Newcastle disease virus or with poly(I):poly(C). In addition, the induced mouse cell clones gave rise to the synthesis of human IFN-beta1. These results suggest the presence of a unique nucleotide sequence in the 1.8 kilobase DNA which is sufficient for the inducer-responsive expression of the human IFN-beta1 gene. (Author abstract) (30 Refs)

2. STUDIES ON THE ACTIVITY OF ALPHA-FETOPROTEIN GENE.

Choi NH, Higashi T
Dept. Biochemistry, Sch. Pharmaceutical Sciences, Showa Univ., 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan
Chem Pharm Bull (Tokyo); 29(11):3311-3319 1981

Purified alpha-fetoprotein (AFP) messenger (m)RNA from rat AH-66 hepatoma cells formed complementary (c)DNA upon incubation in a system with avian myeloblastosis virus RNA-dependent DNA polymerase. The (3H)cDNA had a peak fraction of about 1,000 nucleotide length upon alkali-sucrose gradient centrifugation; AFP cDNA hybridized with AFP mRNA, but not with rat liver catalase mRNA. Thermal denaturation analysis showed a sharp melting profile, indicating a faithful transcription in AFP cDNA:mRNA hybrids. The conformation of the AFP gene was studied by digestion of nuclei of AH-66 cells and rat liver cells with DNAse I or microsomal nuclease. Chromosomal proteins (CP) extracted from chromatin of AH-66 and rat liver cells were similar in comparisons by QAE-Sephadex A-25 chromatography and sodium dodecyl sulfate-polyacrylamide gel electrophoresis. RNA transcripts from intact and reconstituted chromatin of AH-66 cells hybridized with AFP cDNA, but those from rat liver cells did not, indicating that AFP gene is active in AH-66 cells, but suppressed in liver cells. The addition of one of the fractions of AH-66 CP during reconstitution of rat liver chromatin lead to transcription of the AFP gene; no rat liver CP could be found that when added during reconstitution would inhibit transcription of AH-66 AFP gene. (24 Refs)

3. TRANSCRIPTION OF 5 S RNA GENES IN VITRO IS FEEDBACK-INHIBITED BY HELA 5 S RNA.

Gruissem W, Seifart KH
Dept. Molecular, Cellular, and Developmental Biology, Univ. Colorado, Boulder, CO, 80309
J Biol Chem; 257(3):1468-1472 1982

Genes for Xenopus oocyte-type 5 S ribosomal RNA are correctly transcribed in cell-free extracts derived from HeLa cells. At least two factors besides RNA polymerase III are required for the transcription process in somatic cells, one of which has affinity for DNA. The transcription of the oocyte-type 5 S genes can be selectively and completely repressed by purified HeLa 5 S RNA present in the transcription extract, while tRNA represses transcription incompletely and apparently nonspecifically. Weak competition of Xenopus 5 S ribosomal genes for a transcription factor(s) in the presence of HeLa 5 S RNA is discussed in terms of the relative strength of heterologous 5 S gene sequences to bind a transcription factor(s). Nonribosomal-bound 5 S RNA from the cytoplasm can be demonstrated to exist as a 7 S particle. The competition of 5 S RNA genes and 5 S RNA for a transcription factor and the finding of a 7 S particle in HeLa cells suggests a general feedback mechanism of 5 S RNA gene transcription. (Author abstract) (22 Refs)

4. INDUCER-MEDIATED COMMITMENT OF MURINE ERYTHROLEUKEMIA CELLS TO DIFFERENTIATION: A MULTISTEP PROCESS.

Chen ZX, Banks J, Rifkind RA, Marks PA
Soochow Medical Coll., Soochow, People's Republic of China
Proc Natl Acad Sci USA; 79(2):471-475 1982

There are a number of agents which, when added to cultures of murine erythroleukemia cells (MELC), markedly increase the probability of commitment to express the characteristics of terminal erythroid differentiation, including loss of proliferative capacity and increased accumulation of globin mRNA and hemoglobin. Some characteristics of inducer-mediated commitment of MELC to terminal erythroid differentiation were examined by determining the effects of dexamethasone (an inhibitor of inducer-mediated MELC differentiation) and of hemin (an inducer of globin mRNA accumulation). Previously, it was shown that exposure of MELC to hexamethylene-bisacetamide (HMBA) leads to commitment, detectable within 12 hr. MELC cultured with both HMBA and dexamethasone do not express commitment. MELC transferred from culture with HMBA and dexamethasone to cloning medium without these agents express commitment to terminal erythroid differentiation, indicating that MELC retain a 'memory' for some early HMBA-mediated changes leading to commitment which occur even in the presence of the inhibitory steroid. The kinetics of commitment in experiments in which exposure to HMBA is interrupted, or dexamethasone is added to the culture with HMBA, suggest that there is a rate-limiting step early in the commitment process. The memory for this step persists for more than one cell cycle. Addition of hemin to cultures with HMBA and dexamethasone initiates accumulation of globin mRNA but does not reverse the steroid-mediated inhibition of terminal cell division (that is, the cells retain their proliferative capacity). Inducer-mediated MELC commitment is associated with accumulation of the chromatin protein IP25; dexamethasone does not inhibit this accumulation. Accumulation of IP25 may be inducer-related, but it is not sufficient to cause expression of terminal erythroid differentiation. (Author abstract) (49 Refs)

5. INITIATION AND REGULATION OF SIMIAN VIRUS 40 EARLY TRANSCRIPTION IN VITRO.

Lebowitz P, Ghosh PK
Dept. Internal Medicine, Yale Medical Sch., New Haven, CT, 06510
J Virol; 41(2):449-461 1982

We have studied initiation and regulation of early transcription of simian virus (SV40) DNA in vitro by eucaryotic RNA polymerase II, using both a crude HeLa cell extract and a partially purified calf thymus polymerase supplemented with a HeLa cell S100 fraction. Analysis of initiation sites by primer-directed cDNA synthesis and sequencing of cDNA's has revealed that early transcription is initiated at a multiplicity of sites corresponding to the 5' termini of early viral mRNA's. The pattern of in vitro initiation closely resembles the pattern of 5' termini of early mRNA's late in the lytic cycle, with principal initiations between residues 5184 to 5194, upstream from the early Hogness-Goldberg (TATA) sequence, and at residue 5123, well downstream from this sequence. In vitro transcription is initiated to a lesser extent at sites between residues 5150 and 5155, the principal 5' termini of early mRNA's in transformed cells and early in lytic infection, located 21 to 26 nucleotides downstream from the TATA sequence. Initiation occurs at identical sites and with similar efficiencies on form I and linearized DNA templates. There are minor differences in the efficiency of initiation at specific sites by the two transcriptional systems. Studies using a DNA template cleaved just downstream from the TATA sequence and a second template cleaved through a pair of 72-base-pair tandem repeats starting 87 nucleotides upstream from the TATA sequence have revealed that neither the TATA sequence nor the repeats are essential for early transcription in vitro. However, removal of the TATA and upstream sequences shifts initiation of transcription principally to the residue 5123 site. Comparison of the relative efficiencies of transcription on intact wild-type DNA, the two cleaved DNAs, and DNA from a deletion mutant suggests that all or most of the sequences constituting an early promoter lie within the genomic region 60-70 to 140 nucleotides upstream from the principal 5' termini of the early mRNA's. (Author abstract) (43 Refs)

STUDIES OF HETEROGENEOUS NUCLEAR RNA

6. ADENOVIRAL HETEROGENEOUS NUCLEAR RNA IS ASSOCIATED WITH THE HOST NUCLEAR MATRIX DURING SPLICING.

Mariman EC, Van Eekelen CA, Reinders RJ, Berns AJ, Van Venrooij WJ
Dept. Biochemistry, Univ. Nijmegen, Geert Grooteplein Noord 21, 6525 EZ Nijmegen, The Netherlands
J Mol Biol; 154(1):103-119 1982

After infection of HeLa cells with adenovirus type 2, virus-specific heterogeneous nuclear RNA is quantitatively associated with a higher ordered structure, the nuclear matrix. Analysis of this matrix-associated RNA by S1 nuclease mapping showed that precursors as well as processed messenger RNAs from the late region L4 were present. By irradiation of intact cells with ultraviolet light, proteins tightly associated with heterogeneous nuclear RNA can be induced to cross-link with the RNA. Characterization of the cross-linked RNA-protein complexes showed that all viral polyadenylated RNAs (precursors, products and processing intermediates) could be cross-linked to two host proteins, earlier found to be involved in the association of host-specific heterogenous nuclear RNA to the nuclear matrix. Our results thus further support the concept that the nuclear matrix may function in the localization and the structural organization of (viral) heterogeneous nuclear RNA during its processing. (Author abstract) (31 Refs)

7. ADENO-ASSOCIATED VIRUS RNA TRANSCRIPTION IN VIVO.

Marcus CJ, Laughlin CA, Carter BJ
Lab. Experimental Pathology, Natl. Inst. Arthritis, Diabetes, Digestive and Kidney Diseases, NIH, 9000 Rockville Pike,, Bethesda, MD, 20205
Eur J Biochem; 121(1):147-154 1981

We have studied RNA transcripts of the defective parvovirus, adeno-associated virus (AAV) present in poly-(A)rich and poly-(A)free fractions of nuclear and cytoplasmic RNA prepared from cells infected together with a helper adenovirus. Cytoplasmic poly-(A)rich RNA contains three overlapping spliced AAV RNAs having sizes of 3.9 x 10(3), 3.3 x 10(3) and 2.3 x 10(3) base respectively. The nuclear precursors of the RNAs appear to be the coterminal unspliced poly(A)-rich RNAs containing 4.2 x 10(3), 3.6 x 10(3) and 2.6 x 10(3) bases respectively. These unspliced RNAs were also found in the cytoplasm. The nuclear poly(A)-free RNA contained a heterogenous population of AAV RNAs that were generally smaller than 2.3 x 10(3) bases. In addition, the Hirt pellet fraction of the nuclear RNA contained two discrete AAV poly(A)-free RNAs having sizes of 2.5 x 10(3) and 2.8 x 10(3) bases. The 4.2 x 10(3) and 3.6 x 10(3)-base unspliced RNAs are more abundant than the coterminal 3.9 x 10(3) and 3.3 x 10(3)-base spliced RNAs whereas the 2.3 x 10(3)-base spliced RNA is much more abundant than the 2.6 x 10(3)-base unspliced RNA. Thus, the cytoplasmic abundance of the AAV spliced RNAs appears to be controlled in part by the post-transcriptional events of splicing or message stability. We also analyzed the effects of AAV defective-interfering genomes upon AAV transcription. These studies showed that when synthesis of standard AAV genomes was inhibited more than 10-fold by defective-interfering genomes there was no significant effect on the types or amounts of AAV RNA transcripts which accumulated. These observations indicate that interference by defective-interfering genomes occurs mostly at the level of DNA replication rather than transcription. (Author abstract) (24 Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

8. RESTRICTED EXPRESSION OF INTEGRATED PRIMATE TYPE-C VIRUS (GIBBON APE LEUKEMIA VIRUS-SIMIAN SARCOMA VIRUS) PROVIRAL DNA IN NONPRODUCTIVELY INFECTED HUMAN B LYMPHOBLASTS.

Ceccherini Nelli L, Dalla-Favera R, Markham PD, Ruscetti FW, Wong-Staal F, Gallo RC, Reitz MS
(c/o Gallo) Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Virology; 117(1):195-206 1982

Human B-lymphoblast cell lines established from peripheral blood after infection with retroviruses of the simian sarcoma/simian sarcoma associated virus (SSV/SSAV)-gibbon ape leukemia virus (GALV) group generally do not produce detectable virus, even though viral RNA and protein are expressed. We show here by Southern blot and liquid molecular hybridization experiments that most of these nonproducer cultures not producing virus contain apparently complete proviral DNA sequences which lack detectable rearrangements, indicating that restriction of virus replication is not due to obvious proviral lesions. The provirus is often present in only a fraction of the cell population, although the proviral copy number is variable and increases during extensive tissue culture or passage through nude mice. The proviral DNA is integrated into multiple heterogeneous sites in these cells, indicating a polyclonal population. A few of these cell lines have been cloned. Clonal lines have so far originated only from cells which contain proviral DNA and express viral RNA, although they still do not produce complete or infectious virus. Southern blots show that these cells are clonal in origin and contain a complete provirus with two LTRs arranged in the normal orientation. Two viral mRNA species are expressed which are identical in size to those from virus-producing cell lines. The smaller (presumably env) mRNA, like that from virus-producing lines is a spliced transcript which contains both 5'- and 3'-derived sequences. These data strongly suggest that these cells restrict viral replication at some stage later than mRNA synthesis, possibly at the level of protein synthesis or processing. (Author abstract) (15 Refs)

9. COMPARISON OF THE POLYOMA VIRUS EARLY AND LATE PROMOTERS BY TRANSCRIPTION IN VIVO.

Jat P, Cowie A, Kamen R
Transcription Lab., Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London, England
Nucleic Acids Res; 10(3):871-887 1982

Polyoma virus DNA was transcribed in the HeLa whole cell extract in vitro system. Early region transcripts with the same 5'-ends as in vivo mRNAs, located 31 +-2 bp from 'TATA'-boxes, were synthesized by RNA polymerase II. Sequences sufficient for efficient expression of the early promoter were present in a substitution mutant lacking viral DNA from a position 55bp before the principal cap sites. Late region transcripts were synthesized inefficiently. Only one (at nt5129 +-2) of the many late mRNA cap sites functioned as an in vitro initiation point. This was the one 5'-end located 31 +-2 bp from a sequence resembling the 'TATA' consensus. The proportion of late to early region RNA polymerase II transcripts decreased dramatically at suboptimal template concentrations. An hypothesis to explain the regulation of late gene expression in vivo based on these results is proposed. Although linear templates were transcribed only by RNA polymerase II, transcripts with the same sense as late mRNAs and 5'-ends at nt5076 +-2 were produced from superhelical templates by an alpha-amanitin resistant enzyme. (Author abstract) (52 Refs)

10. RESOLVING THE FUNCTIONS OF OVERLAPPING VIRAL GENES BY SITE-SPECIFIC MUTAGENESIS AT A MRNA SPLICE SITE.

Montell C, Fisher EF, Caruthers MH, Berk AJ
Dept. Microbiology, Univ. California, Los Angeles, CA, 90024
Nature; 295(5848):380-384 1982

Early region IA of human adenoviruses encodes a function required for normal induction of early viral genes and virus-induced cell transformation. The region is expressed at early times as two overlapping spliced mRNAs, 12S and 13S, which encode closely related proteins. To distinguish between the functions of these proteins, a single T to G transversion was constructed which prevents splicing of the 12S mRNA. This transversion, in the second base of the 12S mRNA intron, does not alter the protein encoded by the 13 mRNA due to degeneracy in the genetic code. Studies with this mutant demonstrated that only the 13S mRNA encodes the regulatory protein required for normal early gene expression. (Author abstract) (47 Refs)

11. SPECIFIC DIFFERENTIATION EVENTS INDUCED BY ERYTHROPOIETIN IN CELLS INFECTED IN VITRO WITH THE ANEMIA STRAIN OF FRIEND VIRUS.

Koury MJ, Bondurant MC, Duncan DT, Krantz SB, Hankins WD
Div. Hematology, Dept. Medicine, Vanderbilt Univ. Sch. Medicine, Veteran's Admin. Medical Center, Nashville, TN, 37232
Proc Natl Acad Sci USA; 79(2):635-639 1982

Mouse bone marrow cells infected in vitro with the anemia strain of Friend leukemia virus form large clusters (bursts) of erythroblasts after 5 days in culture in methylcellulose medium. Two types of erythroblast populations can be isolated from bursts of infected cells by manipulation of the culture conditions. One type of erythroblast, which is obtained when erythropoietin (EP) is added to the culture, has proliferated and undergoes differentiation to become an erythrocyte. The second type of erythroblast, which is obtained when no EP is added to the culture, is the product of extensive proliferation, but it fails to undergo the terminal stages of erythroblast differentiation. Comparisons of these two types of erythroblasts demonstrate that specific EP effects include changes in the nucleus, cytoplasm, and membrane of the treated cells. Those events of erythroid differentiation shown to be directed by EP were extrusion of the nucleus from the erythroblast, induction of uroporphyrinogen I synthetase activity, increased iron incorporation into protoporphyrin, synthesis of alpha- and beta-globin polypeptides due largely to increased mRNA production, and synthesis and incorporation of spectrin into the cell membrane. In this system, EP promotes these effects without observable stimulation of progenitor proliferation in addition to that caused by the virus alone. Thus, the role of EP in terminal erythrocyte differentiation is not simply that of an erythroid-specific mitogen. (Author abstract) (30 Refs)

12. PROTEINS CONTAINING ONLY HALF OF THE CODING INFORMATION OF EARLY REGION 1B OF ADENOVIRUS ARE FUNCTIONAL IN HUMAN CELLS TRANSFORMED WITH THE HERPES SIMPLEX VIRUS TYPE 1 THYMIDINE KINASE GENE AND ADENOVIRUS TYPE 2 DNA.

Klessig DF, Quinlan MP, Grodzicker T
Dept. Cellular, Viral and Molecular Biology, Univ. Utah, Salt Lake City, UT, 84132
J Virol; 41(2):423-434 1982

We introduced into tk- human 143 cells adenovirus Type 2 (Ad2) genes by transformation with a plasmid (p711) containing both Ad2 sequences and the herpes simplex virus Type 1 (HSV-1) tk gene. p711 contained approximately the left 8% of the Ad2 genome inserted in the HindIII site of pBR322, whereas the fragment of HSV-1 containing the tk gene was inserted in the BamHI site. Three tk+ cell lines were isolated after selection in HAT medium. The arrangement of viral sequences in the three transformants was analyzed by restriction endonuclease digestion and filter hybridization. All three lines contained a single insertion of Ad2 DNA which was present at approximately one copy per cell. The arrangement of Ad2 sequences in these lines was identical to that found in the linear p711 DNA used in the transformation. S1 analysis of the Ad2-specified RNA from two of these lines indicated that the early region 1a mRNA's were synthesized, though in lower amounts than found in lytic infections. These cell lines contained only the left half of early region 1b (4.6 to 11.2), which encoded the 5' portion of the 1b mRNA's. A complex pattern of 1b RNAs was made in these cell lines. Transcription of most of these RNAs began at or near the 1b promoter and proceeded through the 1b sequences into the flanking pBR322, HSV-1, or host sequences. Since many of the RNAs were terminated or spliced in the HSV-1 (anti-sense strand) or pBR322 sequences, new RNA processing sites must be used in the formation of these mRNA's. All three lines fully complemented the 1a deletion mutant Ad5 dl312. Surprisingly, these lines also permitted the growth of 1b deletion mutants (Ad5 dl313 and Ad5 dl434), although the complementation was not always complete. Presumably the new gene product(s) which contained only part of the 1b gene provided most of the essential function(s) required for viral multiplication. Alternatively, the 1b 19-kilodalton protein which was entirely encoded by the adenovirus sequences present in these cell lines was sufficient for viral growth even in the absence of the 1b 5 5-kilodalton protein. (Author abstract) (50 Refs)

13. CHARACTERIZATION OF THE MAJOR EPSTEIN-BARR VIRUS-SPECIFIC RNA IN BURKITT LYMPHOMA-DERIVED CELLS.

Arrand JR, Rymo L
Imperial Cancer Res. Fund Lab., London WC2A 3PX, England
J Virol; 41(2):376-389 1982

Cytoplasmic RNA prepared from five lymphoid cell lines and a Burkitt lymphoma biopsy was radioactively labeled in vitro and hybridized to cloned EcoRI restriction endonuclease fragments of B95-8 Epstein-Barr virus DNA. The results confirmed that the most abundant cytoplasmic RNA species in such cells is specified by a small region of the genome defined by the EcoRI J fragment. Detailed mapping experiments precisely localized these transcripts within the sequence of the rightmost one-third of the EcoRI J fragment. DNA sequencing suggested that this region of the Epstein-Barr virus genome is unable to code for protein. The major early transcripts consisted of two non-polyadenylated RNA species, each about 170 nucleotides in length. They were both transcribed off the same strand of the DNA and showed significant sequence homology with each other. The coding sequences of the two small RNAs contained potential intragenic control regions for RNA polymerase III. (Author abstract) (53 Refs)

14. SEQUENCE COMPLEXITY OF POLYADENYLATED RNA IN HUMAN BREAST CARCINOMA CELLS.

Arya SK
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Int J Biochem; 14(1):19-24 1982

Human breast carcinoma cells (line ZR-75-31; passage 60-80) were harvested from subconfluent monolayers and the complexity of total and polysomal polyadenylate (poly(A)) containing (poly(A)+) RNA was investigated by RNA:complementary (c)DNA and RNA:single-copy (sc) DNA hybridization. Kinetics of poly(A)+ RNA:cDNA hybridization suggested a 3-component solution; the overall sequence complexity of cellular poly(A)+ RNA was apparently about 200,000 kilobases (kb), and of polysomal poly(A)+ RNA about 38,000 kb. Hybridization of polysomal poly(A)+RNA with its cDNA showed a slightly different distribution sequence when cultures were treated with 0.2 ug/ml ovine prolactin for 48 hr. At maximal hybridization attained, 4.8% of sc DNA hybridized with total cellular poly(A)+RNA, and in a similar experiment 1.6% of polysomal poly(A)+RNA hybridized with scDNA. Results of cellular DNA:cDNA hybridization suggest that approx 5% of the sequences in total cellular and 15% of the sequences in polysomal poly(A)+RNA were reiterated transcripts. (26 Refs)

15. ANALYSIS OF HISTONE GENE EXPRESSION DURING THE CELL CYCLE IN HELA CELLS BY USING CLONED HUMAN HISTONE GENES.

Rickles R, Marashi F, Sierra F, Clark S, Wells J, Stein J, Stein G
Dept. Immunology and Medical Microbiology, Univ. Florida, Gainesville, FL, 32610
Proc Natl Acad Sci USA; 79(3):749-753 1982

Although it is generally agreed that histone protein synthesis is restricted to the S phase of the cell cycle - and therefore parallels DNA replication - both transcriptional and posttranscriptional levels of control have been invoked. Using blot hybridization with several cloned genomic human histone sequences representing different histone gene clusters as probes, we have assessed the steady-state level of histone RNAs in the nucleus and cytoplasm of G1 and S phase HeLa S3 cells. The representation of histone mRNA sequences of G1 compared with S phase cells was less than 1% in the cytoplasm and approx 1% in the nucleus. These data are consistent with transcriptional control, but we cannot completely dismiss the possibility that regulation of histone gene expression is, to some extent, mediated posttranscriptionally. If histone gene transcription does occur in G1, the RNAs must either be rapidly degraded or be transcribed to a limited extent compared with S phase. An unexpected result was obtained when a blot of cytoplasmic RNA from G1 and S phase cells was hybridized with lambdaHHG 41 DNA (containing H3 and H4 human genomic histone sequences). Although hybridization with histone mRNAs was observed for RNAs from S phase but not from G1 cells, hybridization with a nonhistone RNA of approx 330 nucleotides present predominantly in G1 was also observed. (Author abstract) (29 Refs)

16. ISOLATION OF ALPHA-FETOPROTEIN MESSENGER RIBONUCLEIC ACID FROM AH-66 ASCITES HEPATOMA CELLS.

Choi NH, Higashi T
Dept. Biochemistry, Sch. Pharmaceutical Sciences, Showa Univ., 1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142, Japan
Chem Pharm Bull (Tokyo); 29(11):3305-3310 1981

The messenger (m)RNA for alpha-fetoprotein (AFP) was isolated from polysomes of AH-66 rat hepatoma cells by extraction of immunoprecipitates and purification by affinity chromatography with oligo(deoxythymidine)-cellulose column. Sodium dodecyl sulfate polyacrylamide gel electrophoresis of AFP gave two mol wt peaks of 72,000 and 74,000; the purified AFP contained 1.5% hexose, 1.5% hexosamine, and 0.9% sialic acid. Electrophoresis of purified AFP mRNA on acid-urea agarose gel suggested a mol wt of 2,700. Purified anti-AFP antibody from anti-rat AFP horse antiserum was reactive against AH-66 ascites fluid, purified rat AFP, and anti-horse IgG rabbit antibody, but not adult rat serum. A quantitative analysis showed that the molar ratio of anti-AFP antibody to rat AFP is approx one at the equivalent point. Purified AFP mRNA translated in the wheat germ S-30 cell-free system was measured by radioactivity incorporated in immunoprecipitates; results indicated that the obtained AFP mRNA was at least 75% pure in terms of messenger activity. (21 Refs)

17. A 3' CO-TERMINUS OF TWO EARLY HERPES SIMPLEX VIRUS TYPE 1 MRNAS.

McLauchlan J, Clements JB
Inst. Virology, Univ. Glasgow, Glasgow G11 5JR, Scotland
Nucleic Acids Res; 10(2):501-512 1982

A 3' co-terminus of two early herpes simplex virus type 1 mRNAs has been identified using the nuclease-51 mapping procedure with cloned virus DNA probes. These mRNAs (5.0 kb and 1.2 kb), located within the genome region 0.56-0.60, are unspliced and are transcribed rightwards on the prototype genome orientation. The position of their 3' ends has been located on the virus DNA sequence and lies downstream from the polyadenylation signal 5'-AATAAA-3'. This hexanucleotide sequence also was present in the complementary DNA strand and was shown to be the polyadenylation signal for a leftwards-transcribed late mRNA. The abundance within the cytoplasm of the 5.0 kb and 1.2 kb mRNAs was investigated. Results indicated that these mRNAs were regulated in concert. It is suggested that sequences at the 3' co-terminus may be involved in their regulation. (Author abstract) (25 Refs)

18. ANALYSIS OF IMMUNOGLOBULIN MRNA IN MURINE MYELOMA CELL VARIANTS DEFECTIVE IN THE SYNTHESIS OF THE LIGHT OR HEAVY POLYPEPTIDE CHAINS.

Wallach M, Ishay-Michaeli R, Givol D, Laskov R
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J Immunol; 128(2):684-690 1982

The immunoglobulin (Ig) mRNA species in spontaneously arisen myeloma cell variants, which lose the ability to synthesize the Ig heavy and/or light chains, were analyzed using the RNA blotting technique. Nick-translated recombinant plasmid clones containing kappa- and gamma-chain sequences were used as hybridization probes. It was found that the MPC 11 clone 4T00.1L1 and the MOPC 21 clone NSI, which are known to produce small quantities of the gamma2b and gamma1 heavy chains, respectively, contained correspondingly small amounts of gamma-mRNA molecules; although the gamma-mRNA of clone 4T00.1L1 was of normal size (1.9 kilo bases [kb]), the gamma-mRNA of clone NSI was of a smaller size (1.3 kb). Reduced quantities of a smaller sized gamma heavy chain mRNA were also found in the MPC 11 clone 66.2 (1.7 kb) and in MOPC 21 clones P3NP (1.7 kb) and 653 (1.7 kb), which do not produce detectable amounts of gamma heavy chains. The only nonproducer clone that seemed to be completely devoid of the gamma-mRNA was clone NP2 (MPC 11). With regard to the kappa-mRNA, the nonproducer MOPC 21 variants P3NP and 653 were found to contain appreciable amounts of smaller or normal-sized kappa-mRNA, respectively. In contrast, the MPC 11 nonproducer clone NP2 did not contain detectable levels of the full-length 1.2 kb kappa-mRNA, even though it did produce the 0.8 kb kappa-mRNA fragment, which is known to be present in all the MPC 11 clones. It would thus appear that most of the myeloma cell variants that lost the ability to produce Ig chains contain reduced to normal quantities of smaller or normal-sized Ig mRNA molecules. These findings indicate that in many of these mutants the respective Ig genes are not fully deleted. (Author abstract) (45 Refs)

19. MESSENGER RNA FOR HUMAN TISSUE PLASMINOGEN ACTIVATOR.

Opdenakker G, Weening H, Collen D, Billiau A, De Somer P
Rega Instituut, Katholieke Universiteit te Leuven, Minderbroedesstraat 10, B-3000 Leuven, Belgium
Eur J Biochem; 121(2):269-274 1982

A human melanoma cell line (Bowes), which secretes extrinsic (tissue-type) plasminogen activator, was used as a source for the preparation of mRNA for extrinsic plasminogen activator. The cells were lysed and total RNA was extracted with the phenol method. A poly(A)-rich RNA fraction was isolated by affinity chromatography on oligo(dT)-cellulose. This preparation was translated by oocytes into (a) protein(s) that had biological activity in the assay for extrinsic plasminogen activator. On sucrose gradient centrifugation the translatable fraction of the RNA migrated with a sedimentation coefficient of approx 19 S, a value compatible with the mol wt of extrinsic plasminogen activator (70,000). The translation product was characterized as being similar to or identical with authentic extrinsic plasminogen activator by the following criteria: (a) serological cross-reactivity with purified extrinsic plasminogen activator in neutralization and immunoprecipitation reactions; (b) plasminogen dependency of fibrinolytic activity and (c) apparent mol wt of 70,000 on sodium dodecyl sulfate/polyacrylamide gel electrophoresis. (Author abstract) (23 Refs)

20. SPONTANEOUS PRODUCTION OF GAMMA INTERFERON AND INDUCED PRODUCTION OF BETA INTERFERON BY HUMAN T-LYMPHOBLASTOID CELL LINES.

Morris AG, Morser J, Meager A
Dept. Biological Sciences, Univ. Warwick, Coventry CV4 7AL, England
Infect Immun; 35(2):533-536 1982

Two human T-lymphoblastoid cell lines, CCRF/CEM and Molt 4, produced beta interferon (IFN-beta) upon infection with Sendai virus. Molt 4, but not CCRF/CEM, spontaneously produced up to 300 U of IFN-gamma per ml, apparently not contaminated with IFN-alpha or -beta. Phytohemagglutinin, a T-cell mitogen, did not stimulate IFN production in these lines. A third T-lymphoblastoid line, CCRF/HSB2, produced no IFN either spontaneously or after infection with Sendai virus or treatment with phytohemagglutinin. The Molt 4 cells contained an mRNA which could be translated by oocytes to give IFN-gamma. Molt 4 cells therefore provide a convenient source of human IFN-gamma and its mRNA for experimental purposes. (Author abstract) (19 Refs)

21. PARTIAL CHARACTERIZATION OF THE MRNA THAT CODES FOR ENKEPHALINS IN BOVINE ADRENAL MEDULLA AND HUMAN PHEOCHROMOCYTOMA.

Comb M, Herbert E, Crea R
Dept. Chemistry, Univ. Oregon, Eugene, OR, 97403
Proc Natl Acad Sci USA; 79(2):360-364 1982

The compounds [Met]enkephalin and [Leu]enkephalin are derived from a protein in bovine adrenal medulla that contains multiple copies of [Met]enkephalin. Here we characterize pro-enkephalin mRNA from bovine and human tissue by use of an oligodeoxynucleotide pentadecamer probe complementary to codons for Tyr-Gly-Gly-Phe-Met ([Met]enkephalin). This probe hybridizes specifically to a species of poly(A)-RNA from adrenal medulla and human pheochromocytoma, (1,400-1,450 bases), and also to [Met]enkephalin-containing pro-opiomelanocortin mRNAs from bovine pituitary (1,200 bases) and from mouse pituitary tumor cells (1,100 bases). A cloned cDNA probe (144 bases) complementary to the region of pro-opiomelanocortin mRNA that codes for lipotropin does not hybridize to the RNA from bovine adrenal medulla, demonstrating that the latter RNA is not pro-opiomelanocortin mRNA. The pentadecamer probe was extended to make cDNA with reverse transcriptase after hybridizing it to adrenal poly(A)-RNA. The sequence of an extended cDNA, 62 bases in length, was found to correspond exactly to that expected from the amino acid sequence of peptide E (a bovine adrenal peptide containing [Met]- and [Leu]enkephalin sequences). This cDNA also forms a specific hybrid with the RNA from bovine adrenal and human pheochromocytoma, confirming that these species of RNA are pro-enkephalin mRNA. (Author abstract) (28 Refs)

22. CDNA CLONES CODING FOR THE HEAVY CHAIN OF HUMAN HLA-DR ANTIGEN.

Lee JS, Trowsdale J, Bodmer WF
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Proc Natl Acad Sci USA; 79(2):545-549 1982

Two cDNA clones, pDRH1 and pDRH2, containing sequences specific for human HLA-DR antigens were isolated from a bank of cDNA clones made from partially purified

HLA-DR mRNA from the human lymphoblastoid cell line Maja. The clones were specific for the Mr 34,000 HLA-DR antigen glycoprotein chain. The identity of these clones was established by (i) their ability to hybridize specifically to HLA-DR mRNA in a positive selection assay; (ii) mRNA species hybridizing to the cDNA clones were expressed in B-cell but not in T-cell or fibroblast cell cultures; and (iii) a nucleotide sequence in the longer clone, pDRH2, could be translated into an amino acid sequence that is identical to the limited NH2-terminal amino acid sequence available for the purified HLA-DR antigen Mr 34,000 chain. Analysis of dNA from human, mouse, and human-mouse somatic cell hybrid lines by Southern transfer of restriction endonuclease digests indicated that the HLA-DR heavy chain is encoded in chromosome 6. This finding is compatible with the location of at least one of the HLA-D/DR heavy chain genes within the HLA region. In addition, the sequences coding for HLA-DR heavy chain appear to be present in only one or a few copies in the genome and to be relatively simple in structure. (Author abstract) (43 Refs)

23. DIFFERENTIAL INDUCTION OF RAT HEPATIC CYTOCHROME P-448 AND GLUTATHIONE S-TRANSFERASE B MESSENGER RNAS BY 3-METHYLCHOLANTHRENE.

Pickett CB, Telakowski-Hopkins CA, Donohue AM, Lu AY, Hales BF

Dept. Biochemical Regulation, Merck Sharp and Dohme Res. Lab., Rahway, NJ, 07065

Biochem Biophys Res Commun; 104(2):611-619 1981

The in vitro levels of functional rat liver cytochrome P-448 and glutathione S-transferase B messenger(m)RNAs in response to 3-methylcholanthrene (3-MC) were quantitated by polyadenylate-RNA translation and specific immunoprecipitation with rabbit anti-cytochrome P-448 IgG. Administration of 40 mg/kg 3-MC to rats resulted in an accumulation of functional mRNAs specific for cytochrome P-448 and glutathione S-transferase B; 3-MC administration lowered rat serum albumin mRNA. Fluorograms of sodium dodecyl sulfate polyacrylamide gel electrophoresis revealed selective immunoprecipitation of two polypeptides of mol wt 55,000 and 54,000 daltons, respectively, from the in vitro translation system programmed with total liver polyadenylated-RNA from 3-MC-treated rats. No such polypeptides were precipitated from the translation system of untreated rats. Similar analysis revealed two primary translation products of glutathione S-transferase B, of 29,000 and 27,000 dalton mol wt, which were markedly more concentrated in the translation mixtures from 3-MC-treated rats. The elevation of immunoreactive cytochrome P-448 and glutathione S-transferase B after 3-MC treatment can be totally accounted for by increases in the level of mRNA coding the proteins. (18 Refs)

STRUCTURE AND LEVELS OF RIBOSOMAL RNA

24. THE RAT XC SARCOMA CELL LINE: RIBOSOMAL RNA GENE AMPLIFICATION AND BANDED KARYOTYPE.

Tantravahi U, Erlanger BF, Miller OJ

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Cancer Genet Cytogenet; 5(1):63-73 1982

Ribosomal RNA gene amplification has been demonstrated in the rat XC sarcoma cell line. Cells of this rat line have a fairly stable karyotype with several unusual features, which have been clarified by in situ hybridization, silver staining, and binding of antibodies to 5-methylcytosine. There are one or two tiny acrocentric chromosomes containing transcriptionally active 18S and 28S ribosomal RNA (rRNA) genes. The short arm of one chromosome No 12 has been replaced by a GC-rich, C-band negative, differentially staining region (DSR) containing an increased number of rRNA genes; most of these are transcriptionally inactive and located in regions containing highly methylated DNA. The short arm of a small chromosome, probably a No 20, has been replaced by a GC-rich, C-band negative, homogenously staining region (HSR) that presumably represents amplification of a DNA sequence other than the 18S and 28S rRNA coding sequences. The DNA in this HSR is not enriched in 5-methylcytosine and neither is that in the HSRs of methotrexate-resistant Syrian hamster cells. (Author abstract) (40 Refs)

25. SEQUENCING PSORALEN PHOTOCHEMICALLY REACTIVE SITES IN ESCHERICHIA COLI 16 S RRNA.

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Dept. Biophysics and Medical Physics, Univ. California, Berkeley, CA, 94720

Anal Biochem; 119(1):86-89 1982

The photochemical modification of 16 S rRNA by longwave ultraviolet light in the presence of hydroxymethyltrimethyl psoralen (HMT) produces uridine-psoralen adducts. Psoralen-modified 16 S rRNA is primed with a 3'-proximal restriction fragment and copied with reverse transcriptase. The average length of th cDNA transcripts decreases as the number of covalently bound psoralen adducts on the template RNA increases. Adducts stop reverse transcriptase and abbreviated cDNAs terminate at the positions of the lesions. The cDNA reverse transcripts of psoralen-reacted 16 S rRNA are electrophoresed in parallel with a dideoxy sequence (Sanger method) which uses the same restriction fragment as a primer. The psoralen-induced cDNA stops are found to be highly localized hot spots. In the 150-nucleotide sequence investigated at sequence resolution, two hot spots for psoralen reaction are found. In both cases the psoralen-induced stops are at UpU sequences near the bases of predicted hairpins. (Author abstract) (13 Refs)

26. STUDY ON THE MOLECULAR MECHANISM OF HYDRAZINE SULFATE ACTION ON CERTAIN EXPERIMENTAL TUMORS.

Burova TM, Seits JF
N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(11):56-59 1981

In in vitro experiments hydrazine sulfate has no effect on the distribution and level of cRNA basic fractions in Zajdela's hepatoma ascitic cells, lymphoma NK/Ly, Ehrlich carcinoma as well as the liver of tumor-bearing animals. HS in concentrations of 10.50 and 100 ug/ml of medium was found to markedly suppress the biosynthesis of ribosomal RNA of Zajdela's hepatoma ascitic cells as well as the ascitic cells and liver of rats with Ehrlich carcinoma. (Author abstract) (8 Refs) (In RUS)

STRUCTURE AND LEVELS OF TRANSFER RNA

27. DOES CADMIUM ADMINISTRATION CHANGE PEPTIDE ELONGATION IN RAT LIVER?

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Dept. Biology, York Univ., 4700 Keele St., Downsview (Toronto), Ontario M3J 1P3, Canada
Environ Res; 27(1):36-45 1982

Female rats received two consecutive daily injections of Cd++ (11 micromole/kg body wt) as cadmium chloride. The liver was removed 24 hr later and homogenate fractions were tested for peptide synthesis. The incorporation of [14C]phenylalanyl-tRNA into peptide and the binding of phenylal anyl-tRNA to ribosomes, ie, elongation factor 1 activity, were significantly increased in the pH 5 supernatant fraction from liver of treated rats compared to control rats. When elongation factor 1 was separated from elongation factor 2 by gel filtration, each of the factors exhibited increased peptide-synthesizing activity in preparations from the cadmium-treated rats. (Author abstract) (29 Refs)

28. COMPARISON OF PROTEIN SYNTHESIS BY LYMPHOCYTES FROM BLOOD OF DONORS AND PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

Morozova EO, Blinov MN
Inst. Hematology and Blood Transfusion, Leningrad, USSR
Vopr Onkol; 27(12):28-33 1981

An assay of lymphocyte ribosomes in blood of donors and patients with chronic lymphocytic leukemia established the normal level of ribosomes in 11 cases and half that value in 6 cases of leukemia. The decreased level of ribosomes in cells was largely registered at the terminal stage of the disease. The 14C-leucine uptake by leukemic lymphocytes was reduced two- to three-fold while the relative level of 14C-leucyl-tRNA in diseased and normal cells was identical. The rate of lymphocyte protein synthesis was lowered in a wide range (2-8-fold), in most of patients (7 out of 8). The rate of protein synthesis (radioactivity of acid insoluble fraction per mg of ribosomes) was half the normal value and constant in leukemic lymphocytes. An important role of ribosome level in protein biosynthesis regulation in the course of disease progression is suggested. (Author abstract) (25 Refs) (In RUS)

29. TRNA PRECURSOR TRANSCRIBED FROM A MUTANT HUMAN GENE INSERTED INTO A SV40 VECTOR IS PROCESSED INCORRECTLY.

Zasloff M, Santos T, Hamer DH
Genetics and Biochemistry Branch, Natl. Inst. Arthritis, Diabetes, Digestive and Kidney Diseases, NIH, Bethesda, MD, 20205
Nature; 295(5849):533-535 1982

Functional properties of the human variant initiator transfer (t)RNA gene within an intact cell were assayed by studying its transcription from a simian virus 40 (SV40) recombinant during lytic infection of African green monkey kidney cells. Structure of the SV40-tRNAiMet recombinant (SVtm) used contained a 1.15-kilobase fragment of human genomic DNA harboring a single tRNAiMet gene. Resulting viral stocks were used in the study. Total cytoplasmic and nuclear RNA were recovered from the infected cells and analyzed. Cytoplasmic and nuclear fractions from SVtm-infected cells contained a single low-mol wt species approx 89 nucleotides long. The RNA species accumulating in the SVtm infection was analyzed by classical fingerprinting techniques. The transcript was a precursor of the variant tRNAiMet. Only a preliminary analysis of base modification within the precursor was performed. Hybridization of equal amounts of gel-purified tRNA from SVtm and control infections to filter bound tRNAiMet DNA occurred at approx equal rates and reach ed max level of hybridization of approx 1% of the input radioactivity. Results indicate that conversion of the mutant precursor to mature tRNA does not occur with any significant efficiency, suggesting that mutations within eukaryotic tRNA genes may be more prevalent than assumed from the limited sequence variation observed in mature tRNA species. (22 Refs)

30. QUEUINE HYPOMODIFICATION OF TRNA INDUCED BY 7-METHYLGUANINE.

Elliott MS, Trewyn RW
Dept. Physiological Chemistry, Ohio State Univ., Columbus, OH, 43210
Biochem Biophys Res Commun; 104(1):326-332 1982

Transfer RNA (tRNA) isolated from Chinese hamster embryo (ChH) cells transformed by chronic exposure to 7-methylguanine (7-MG) was queuine hypomodified for queuine (Q) according to assay by Escherichia coli tRNA:guanine transglycosylase, but that transformed by 1-methylguanine (1-MG) was not. 7-MG was also more effective than 1-MG in inhibiting rabbit erythrocyte tRNA:guanine transglycosylase. The role of increased endogenous methylpurines in inducing the Q-modification of tRNA associated with neoplasia is discussed. (22 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

31. ANTITUMOR AGENTS XLVII: THE EFFECTS OF BISBRUSATOLYL MALONATE ON P-388 LYMPHOCYTIC LEUKEMIA CELL METABOLISM.

Hall IH, Liou YF, Lee KH, Okano M, Chaney SG
Div. Medicinal Chemistry, Sch. Pharmacy, Univ. North Carolina at Chapel Hill, Chapel Hill, NC, 27514
J Pharm Sci; 71(2):257-262 1982

Bisbrusatolyl malonate, which was shown previously to be active against P-388 lymphocytic leukemia cell growth, was investigated for inhibitory effects on nucleic acid and protein synthesis. DNA and RNA synthesis as well as protein synthesis were markedly inhibited at 10, 25 and 50 umole final concentrations in vitro. The major sites of inhibition of nucleic acid synthesis appeared to be DNA polymerase, messenger RNA polymerase and transfer RNA polymerase, orotidine-5'-monophosphate decarboxylase, phosphoribosyl pyrophosphate amino transferase, and dihydrofolate reductase. Moderate inhibition of nucleotide kinase activities and oxidative phosphorylation processes occurred after drug treatment. Cyclic adenosine monophosphate levels were reduced. Protein synthesis was inhibited during the elongation step of peptide synthesis. The data suggested that bisbrusatolyl malonate interfered with the peptide bond formation. However, the ongoing polypeptide synthesis must be completed before the drug can bind to the ribosome effectively. (Author abstract) (41 Refs)

32. ISOLATION OF NUCLEOLAR METHYLASE PRODUCING ONLY 5-METHYLCYTIDINE IN RIBOSOMAL RNA.

Ohara M, Higashi K, Kuchino Y
(c/o Higashi) Dept. Biochemistry, Sch. Medicine, Univ. Occupational and Environmental Health, Kitakyushu 807, Japan
Biochem Biophys Res Commun; 104(1):241-246 1982

A purified RNA methylase taken from isolated nucleoli of Ehrlich ascites tumor cells of mice was studied. The preferential localization of this enzyme and its high substrate specificity for ribosomal RNA suggest that it is one of the base-specific methylases for ribosomal RNA, which is actually engaged in the maturation process of ribosomes in the nucleoli. (12 Refs)

OTHER RELATED STUDIES

33. REACTIONS OF VINYL CHLORIDE WITH RNA AND DNA OF VARIOUS MOUSE TISSUES IN VIVO.

Bergman K
Toxicology Lab., Natl. Food Admin., Box 622, S-751 26 Uppsala, Sweden
Arch Toxicol; 49(2):117-129 1982

The irreversible binding of 14C-vinyl chloride metabolites to RNA and DNA of mouse brain, lung, liver, kidney, spleen, pancreas, and testes after a single ip injection has been studied. Hydrolysates of nucleic acids from selected organs were separated on Aminex A6 for quantitation of alkylation products. Radioactivity in nucleic acids was registered in all of the studied organs with the exception of brain. RNA from spleen, pancreas and liver, and DNA from spleen and liver contained the highest amounts of radioactivity. In nucleic acids from spleen and pancreas, both organs of high metabolic activity, the entire radioactivity was found metabolically incorporated as C1-fragments. In RNA of kidney and liver, a large part of the radioactivity was also present as incorporated C1-fragments, but 3,N4-ethenocytidine (in kidney) as well as 1,N6-ethenoadenosine and 1,N6-ethenoadenine (in kidney and liver) were identified as alkylation products. In liver DNA, incorporation of C1-fragments was insignificant, indicating different interactions of vinyl chloride metabolites (C1-fragments and alkylating products) with RNA and DNA. The elution profiles of radioactivity in hydrolysates of liver DNA were dominated by an alkylation product of unknown structure (probably a derivative of deoxyguanosine). Possibly, 1,N6-ethenodeoxyadenosine and 1,N6-ethenoadenine were also present in liver DNA. The results are consistent with the ability of viny chloride to act as a multipotent carcinogen by alkylation of DNA in several tissues. (Author abstract) (45 Refs)

34. INDUCTION OF SPECIFIC CELL-MEDIATED CYTOTOXICITY IN VITRO BY MEANS OF RNA ISOLATED FROM ALLOGRAFTED MICE.

Holan V, Lipoldova M, Zadrazil S, Hasek M
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 163 37 Praha, Czechoslovakia
Folia Biol (Praha); 27(6):422-426 1981

Immune RNA was prepared by sensitization of B10.A mice with allogeneic skin grafts from C57BL/10Sn mice and extraction from spleens and lymph nodes in cold phenol-chloroform-isoamyl alcohol. The RNA extracts induced specific cell-mediated immunity in vitro in lymphocytes of normal B10.A mice, demonstrated by 3H-thymidine microcytoxicity assay in surviving cells of MC11 sarcoma induced in B10 mice or in cells of two Rous sarcoma virus-induced tumors in Wistar rats or DBA mice. The RNA immunospecific cytotoxicity persisted after deoxyribonuclease and pronase treatment but not after ribonuclease treatment, indicating that RNA activity is involved in the induction process. (16 Refs)

35. ISOLATION OF A PURE U1 SNRNP FROM HELA CELLS.

Sri-Widada J, Assens C, Liautard JP, Jenteur P, Brunel C
Laboratoire de Biochimie, Centre Paul Lamarque, 2 avenue Bertin Sans, BP 5054, 34033 Montpellier Cedex, France
Biochem Biophys Res Commun; 104(2):457-462 1981

Ribonucleoprotein labeled with 32P and containing heterogenous nuclear RNA (hnRNP) from HeLa cells were used as a source for purified uridine(U)1 RNA still in ribonucleoprotein form. Centrifugation using cesium chloride and sucrose in the presence of the moderately strong anionic detergent sarkosyl yielded a small nuclear (sn) U1 RNP which had a protein complement electrophoretically identical to that of a mixture of snRNP containing several U species. The functional specificity of snRNP apparently depends upon the snRNA component. (12 Refs)

36. REGULATION OF CASEIN GENE EXPRESSION IN HORMONE-DEPENDENT MAMMARY CANCER.

Rosen JM, Supowit SC, Gupta P, Yu LY, Hobbs AA, Dao TL, Topp, Hilf
Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
Banbury Rep; 8:397-424 1981

Structure, organization, and expression of the casein gene (CG) family and the alpha-lactalbumin gene in the normal mammary gland, and altered regulation of CG expression and gene expression in general in hormone-dependent mammary cancer, were studied. Milk protein structural genes, hormonal regulation of milk protein messenger RNA accumulation in rat mammary gland organ culture, milk gene organization and chromosomal localization, CG expression in hormone-dependent mammary cancer, methylation patterns of the CG, DNA rearrangement in mammary tumors (MT), and expression of unique single-copy DNA sequences in 7,12-dimethylbenz(a)anthracene-induced MT are reviewed. New approaches may help explain the regulation of differentiated function in the normal mammary gland and deviation of the mechanisms in hormone-dependent breast cancer. (38 Refs)

37. LONG TERMINAL REPEATS OF ENDOGENOUS MOUSE MAMMARY TUMOR VIRUS CONTAIN A LONG OPEN READING FRAME WHICH EXTENDS INTO ADJACENT SEQUENCES.

Kennedy N, Knedlitschek G, Groner B, Hynes NE, Herrlich P, Michalides R, Van Ooyen AJ
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Nature; 295(5850):622-624 1982

The integrated DNA copies (proviruses) of RNA tumor virus genomes are flanked by long terminal repeat (LTR) sequences, which are generated by the duplication of segments present at both ends of the viral RNA. LTRs vary in length from 330 to 1,328 base pairs (bp). The primary viral transcript starts in the left LTR (L-LTR) and terminates in the right LTR (R-LTR). We have now sequenced both LTRs from an inherited (endogenous) mouse mammary tumor virus (MMTV) of the GR strain. This provirus, which is one of five present in the haploid genome of GR mice, does not produce virus and is not identical with the exogenous MMTV of GR mice. The provirus (GR40) could nevertheless be transcribed and its transcription hormonally regulated after cloning and transfection into mouse L cells. The LTRs are identical and exhibit the following features: a terminal inverted six-bp repeat, a Goldberg-Hogness (TATAAA) sequence, sequences which have been implicated in polyadenylation and the termination of transcription, and an open reading frame. The open reading frame of the R-LTR starts at the env/LTR junction and encodes a 36,700-mol wt (Mr) protein. The open reading frame of the L-LTR extends into the adjacent mouse sequence. A host sequence of six bp at the site of integration into the mouse chromosome is directly repeated. (Author abstract) (31 Refs)

38. ISOLATION AND PURIFICATION OF RAT HEPATOMA NUCLEI ACTIVE IN THE TRANSPORT OF MESSENGER RNA IN VITRO.

Jacobs H, Birnie GD
Div. Biology, California Inst. Technology, Pasadena, CA, 91125
Eur J Biochem; 121(3):597-607 1982

A variety of procedures for obtaining metabolically active nuclei from rat hepatoma tissue-culture (HTC) cells has been explored. All gave preparations which were, to a greater or lesser extent, contaminated with cytoplasmic RNA, which appeared to be absorbed non-specifically during the lysis of the cells. A medium containing spermidine, monovalent and divalent cations, and cytosol has been defined in which the integrity of the isolated nuclei was maintained during incubation in vitro. The release of steady-state-labeled and pulse-labeled RNA from HTC cell nuclei during incubation in this medium has been studied. The transport of both was dependent on ATP and cytosol, but was distinguishable by the kinetics and by the fact that only the transport of pulse-labeled RNA appeared to involve hydrolysis of ATP. Transported RNA included ribosomal RNA and messenger-like RNA as judged by criteria of size, oligo(dT)-cellulose binding, and organization into ribonucleoproteins. A large proportion of the cytoplasmic RNA which adhered to the nuclei was also released during incubation in vitro. Although the poly(A)-rich RNA transported in vitro was contaminated with poly(A)-rich RNA sequences arising from non-specific leakage of nuclear RNA and from the release of nucleus-adherent cytoplasmic RNA, the extent of this contamination was comparatively small (10% and 10-15% by weight respectively). The transported poly(A)-rich RNA has been shown to consist of a complex mixture of sequences at heterogeneous abundances, resembling polysomal poly(A)-rich mRNA from HTC cells. The pattern of relative abundances of the sequences in transported poly(A)-rich RNA was intermediate between that of polysomal and nuclear poly(A)-rich RNAs, and indicated that some degree of sequence-specific selection of processing, or transport, or both, can be maintained in isolated nuclei. Sequence-specific selection in vitro at the level of individual poly(A)-rich RNA sequences was detected using cloned cDNAs for poly(A)-rich polysomal RNA sequences. (Author abstract) (55 Refs)

39. THE EFFECT OF LH1, AN AMINOACYL-STEROID, ON CULTURED HEPATOMA CELLS.

Giesen EM, Beck JP, Beck G, Nguyen-Dang T
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Cancer Biochem Biophys; 5(4):233-238 1981

LH1, synthesized from 3alpha-amino-5-alpha-pregnane-20-one and N-protected glycine, was used in experiments on HTC cells from clone 7288C of Morris hepatoma in the rat. LH1 penetrated rapidly into cells, at a rate comparable to that of dexamethasone. LH1 exerted a powerful cytoxic effect on HTC cells: half maximal growth inhibition after 1 day was obtained at 15 ug/ml, and after 3 days at 6 ug/ml; 53 ug/ml killed all cells after 1 day, and 30 ug/ml killed all cells after 2-3 days. Logarithmically growing cells were more sensitive than quiescent cells. DNA and RNA synthesis, measured by (3H)thymidine and (3H)uridine incorporation, respectively, were inhibited reversibly below a threshold concentration of 30 ug LH1/ml of cell suspension. LH1 has even more severe inhibitory effects on protein synthesis, and the threshold concentration is lower, suggesting that DNA and RNA synthesis effects may be secondary (low LH1 concentration) or due to a different mechanism of action (high LH1 concentration). (14 Refs)

40. EUKARYOTIC MRNA CAPPING ENZYME-GUANYLATE COVALENT INTERMEDIATE.

Venkatesan S, Moss B
Lab. Biology of Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(2):340-344 1982

Incubation of HeLa cell mRNA guanylyltransferase (GTP:mRNA guanylyltransferase, EC 2.7.7.50) with [alpha-32P]GTP and a divalent cation in the absence of an RNA acceptor results in the formation of a covalent enzyme-guanylate complex. The complex, after purification by phosphocellulose chromatography, can transfer its bound GMP moiety to pyrophosphate, regenerating GTP, or to the 5'-diphosphate end of poly(A), forming a cap structure G(5')pppA(pA)n. The GMP-polypeptide has a mol wt of 65,000 and is stable to heating in the presence of sodium dodecyl sulfate. On the basis of the alkali-stable and acid-labile nature of the bond and its susceptibility to nucleophilic attack by hydroxylamine at low pH, the GMP-po lypeptide linkage appears to be a phosphoamide bond. After digestion with trypsin, a single GMP-peptide was resolved by two-dimensional electrophoresis and chromatography. (Author abstract) (29 Refs)

41. ISOLATION OF A TRANSFORMATION-DEFECTIVE DELETION MUTANT OF MOLONEY MURINE SARCOMA VIRUS.

Evans LH, Duesberg PH
(c/o Duesberg) Dept. Molecular Biology, Univ. California, Berkeley, CA, 94720
J Virol; 41(2):735-743 1982

A transformation-defective (td) deletion mutant of Moloney murine sarcoma virus (td Mo-MSV) and a transforming component termed Mo-MSV 3 were cloned from a stock of clone 3 Mo-MSV. To define the defect of the transforming function, the RNA of td Mo-MSV was compared with those of Mo-MSV 3 and of another transforming variant termed Mo-MSV 124 and with helper Moloney murine leukemia virus (Mo-MuLV). The interrelationships among the viral RNAs were studied by fingerprinting and mapping of RNase T1-resistant oligonucleotides (T1-oligonucleotides) and by identification of T1-oligonucleotides present in hybrids formed by a given viral RNA with cDNA's made from another virus. A comparison of td Mo-MSV sequences with either Mo-MSV 124 or Mo-MSV 3 indicated directly, in a fashion similar to the deletion analyses which defined the src gene of avian sarcoma viruses, that Mo-MuLV-unrelated sequences of Mo-MSV are necessary for transformation. A definition of transformation-specific sequences of Mo-MSV by deletion analysis confirmed and extended previous analyses which have identified Mo-MuLV-unrelated sequences in Mo-MSV RNA and other studies which have described transformation of mouse 3T3 fibroblasts upon transfection with DNAs containing the Mo-MSV-specific sequence. (29 Refs)

42. INHIBITION OF THE RELEASE OF VIRION-ASSOCIATED MURINE LEUKEMIA VIRUS GENOMIC RNA BY VESICULAR STOMATITIS VIRUS.

Chan JC, Mohr MD, Knesek JE, Bowen JM, East JL

Dept. Molecular Carcinogenesis and Virology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030

Intervirology; 16(3):191-200 1981

The genomic RNAs of murine leukemia virus (MuLV) and vesicular stomatitis virus (VSV) were distinguishable based on a difference in sedimentation coefficient, polyadenylic acid content, and nucleotide sequence homology. Applying these biochemical characteristics, we found that the release of virion-associated MuLV genomic RNA from virus-producing cells was inhibited by VSV as early as 2 hr after superinfection. This finding offers an explanation to our previous inability to detect MuLV (VSV) pseudotype formation during mixed infection with VSV and MuLV. (Author abstract) (39 Refs)

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RNA

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RNA TRANSCRIPTION/ SYNTHESIS

1. EXPRESSION OF A CLONED ADENOVIRUS GENE IS INHIBITED BY IN VITRO METHYLATION.

Vardimon L, Kressmann A, Cedar H, Maechler M, Doerfler W
(c/o Doerfler) Inst. Genetics, Univ. Cologne, Weyertal 121, 5000 Cologne, W. Germany

Proc Natl Acad Sci USA; 79(4,part1):1073-1077 1982

In many viral and nonviral eukaryotic systems, an inverse correlation has been observed between the extent of DNA methylation at 5'-C-C-G-G-3' sites and the extent of expression of specific genes as mRNA. The E2a region of adenovirus serotype 2 (Ad2) DNA encodes the Ad2-specific DNA-binding protein required for viral DNA replication. In three lines of

Ad2-transformed hamster cells (HE1, HE2, and HE3). multiple copies of the major part of the Ad2 genome persist in an integrated state. Cell lines HE2 and HE3 do not express the DNA-binding protein whereas line HE1 does so. It has been shown that, in cell line HE1, all 5'-C-C-G-G-3' (Hpa II/Msp I) sites in the E2a region remain unmethylated. Conversely, in lines HE2 and HE3 lacking expression of the E2a region all Hpa II sites are methylated. The cloned E2a region of Ad2 DNA, the HindIII A fragment in pBR322, was methylated in vitro by using Hpa II DNA methyltransferase (5'-C-C*G-G-3') or was left unmethylated. In vitro methylation did not break or nick supercoiled circular DNA. Methylated or unmethylated DNA was then microinjected into the nuclei of Xenopus laevis oocytes, and the subsequent synthesis of Ad2-specific RNA was monitored. In vitro-methylated DNA remained in the methylated state for 24 hr on microinjection into nuclei of Xenopus oocytes; unmethylated DNA remained unmethylated. When the injected DNA had been methylated by using Hpa II DNA methyltransferase, Ad2-specific RNA was not synthesized as late as 24 hr after microinjection. Unmethylated DNA was readily expressed into Ad2-specific RNA. As an internal control, unmethylated histone genes (h22 DNA) from sea urchin were microinjected together with methylated E2a DNA from Ad2. Ad2-specific RNA was not found; h22 DNA-specific RNA was readily detected. This finding ruled out nonspecific inhibitory effects in the methylated DNA preparation. It was also shown that transcription of the unmethylated HindIII A fragment of Ad2 DNA in Xenopus oocytes was initiated on the late promoter of the E2a region. The same promoter was used in productively infected KB cells. Methylation by BsuRI methylase (5'-G-G-C*C-3') did not inactivate the HindIII A fragment. These results provide evidence for the notion that methylated sequences at highly specific sites are involved in the regulation of gene expression. The actual nature of the regulatory signal is not yet understood. (Author abstract) (50 Refs)

2. TRANSCRIPTION AND ACCURATE POLYADENYLATION IN VITRO OF RNA FROM THE MAJOR LATE ADENOVIRUS 2 TRANSCRIPTION UNIT.

Chen-Kiang S, Wolgemuth DJ, Hsu MT, Darnell JE
Memorial Sloan Kettering Cancer Center, New York, NY, 10021
Cell; 28(3):575-584 1982

Nucleoprotein complexes with in vitro transcription activity were isolated from HeLa cells late in lytic infection with Adenovirus type 2 (Ad2). Both polymerase II and polymerase III were active in these extracts, and greater than 85% of the labeled RNA was Ad2-specific. Electrophoretic analyses and Southern blot analyses demonstrated that RNA complementary to the entire 30 kb late transcription unit including RNA near the presumed termination site was synthesized. The addition of DRB (5,6,dichloro-1-beta-D-ribofuranosyl-benzimidazole) in vivo prior to the isolation of the complexes resulted in accumulation of polymerase II at the promoter proximal sites, but nascent chains started in vivo in DRB were successfully elongated in vitro. Approx 10% of the RNA labeled in vitro contained poly(A), and the length of poly(A) was very similar to that of nuclear RNA isolated from Ad2-infected cells. The in vitro sites of poly(A) addition were specific-labeled poly(A)-terminated RNA molecules ended at a point on the genome coincident with previously mapped poly(A) sites of mRNAs produced in vivo. In addition, the polyadenylation enzyme (or enzymes) cosediment with the nucleo-protein complexes during sucrose gradient centrifugation since gradient purified complexes synthesize poly(A) containing RNA in vitro in the absence of any added nuclear extract. (Author abstract) (63 Refs)

3. THE PLUS-STRAND LEADER RNA OF VSV INHIBITS DNA-DEPENDENT TRANSCRIPTION OF ADENOVIRUS AND SV40 GENES IN A SOLUBLE WHOLE-CELL EXTRACT.

McGowan JJ, Emerson SU, Wagner RR
Dept. Microbiology, Univ. Virginia, Sch. Medicine, Charlottesville, VA, 22908
Cell; 28(2):325-333 1982

In an attempt to determine the mechanism (or mechanisms) by which vesicular stomatitis virus (VSV) kills cells, products of VSV trarscription were tested in a cell-free system for their capacity to inhibit transcription of SV40 DNA and plasmids containing adenovirus late promoter and adenovirus-associated RNA genes. VSV RNA transcripts and other RNAs were compared for their capacity to suppress transcription of these DNA templates by RNA polymerases and cofactors present in the HeLa-cell extract system. Relatively low concentrations of the plus-strand leader RNA made in vitro from the 3' end of the wild-type VSV genome were found to inhibit initiation of transcription catalyzed by both RNA polymerase II and RNA polymerase III. Polyadenylated VSV messengers and other natural and synthetic RNAs also caused some inhibitory effects on in vitro transcription from DNA templates, but only at extremely high concentrations. Compared with the wild-type plus-strand RNA leader, the leader RNA synthesized in vitro by defective-interfering VSV showed only limited capacity to inhibit RNA synthesis on adenovirus and SV40 DNA templates and only at concentrations at least 30 times greater than that of the wild-type leader. The existence of nucleotide sequences in wild-type leader RNA, not present in defective-interfering leader RNA, that could recognize and block promoters, polymerases or protein cofactors is discussed. (Author abstract) (36 Refs)

4. EVIDENCE AGAINST INVOLVEMENT OF HOST TRANSCRIPTION IN THE REPLICATION OF VACCINIA AND HERPES SIMPLEX VIRUSES.

Silver M, Dales S
(c/o Dales) Cytotobiology Group, Dept. Microbiology and Immunology, Univ. Western Ontario, London, Ontario N6A 5C1, Canada
Virology; 118(1):214-218 1982

Vaccinia and herpes simplex viruses are unable to multiply in cells treated with the toxin alpha-amanitin, which specifically blocks host transcription involving RNA polymerase II (pol II). However, these agents are replicated in host cells made nonfunctional by intense gamma irradiation when RNA synthesis, including poly(A)-containing RNA and induction of biological functions, exemplified by the antiviral state, are inhibited. From this and previous evidence it is concluded that requirement for pol II or subunit(s) thereof by pox- and herpesviruses is probably related to transcription from the viral, not the host genome. (Author abstract) (11 Refs)

5. THE UVRB GENE OF ESCHERICHIA COLI HAS BOTH LEXA-REPRESSED AND LEXA-INDEPENDENT PROMOTERS.

Sancar GB, Sancar A, Little JW, Rupp WD
Dept. Therapeutic Radiology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Cell; 28(3):523-530 1982

We have found that the uvrB gene of Escherichia coli is transcribed from at least two promoters, which we call P1 and P2. Transcription from P1 begins with an ATP at +1, and transcription from P2 begins primarily with a GTP at-31. A binding site for the lexA protein (LEXA), located between the-35 sequence and Pribnow box of P2, regulates transcription from this promoter. In vitro, LEXA inhibits transcription from P2 but has no detectable effect on transcription from P1. A third promoter, P3, was also detected at-341; transcription from P3 is toward uvrB but terminates in vitro in the region of the LEXA binding site. The binding of LEXA to P2 inhibits transcription from the P3 promoter even though several hundred nucleotides separate the two promoters. The data suggest that a transcribing RNA polymerase stalls when it reaches the repressor-operator complex but remains bound to the DNA, causing a jamming of RNA polymerases between P3 and the repressor-operator complex at P2. The physiological significance of P3 is unknown. (Author abstract) (48 Refs)

6. THE EFFECT OF HYPERTHERMIA ALONE OR IN COMBINATION WITH ACTINOMYCIN D ON THE RNA METABOLISM OF SOLID TUMORS IN CHILDREN.

Willnow U
Clinic Pediatric Surgery, Section Medicine, Karl-Marx-Univ., 7021 Leipzig, E. Germany
Neoplasma; 28(6):721-727 1981

The incorporation of 3H-uridine into the RNA was studied under normothermia 37 C/120 min, hyperthermia 42.5 C/120 min, and both in combination with Actinomycin D by an autoradiographic in vitro method in 19 solid tumors of children: 6 Wilms' tumors, 5 neuroblastomas, 4 osteogenic sarcomas, and 4 different tumors. Hyperthermia invariably reduces the 3H-uridine incorporation into RNA by 11.7-86.4%, with an av of 47.5%. Actinomycin D consistently inhibits the 3H-uridine incorporation between 27.7 and 99.8% with the av inhibition of 62.0% being far greater than that recorded for hyperthermia. The highest degree of 3H-uridine incorporation inhibition is obtained using hyperthermia in combination with Actinomycin D. The inhibition varies from 45.5-99.8%, with an av of 81.4%. In spite of the general regularity, the effect of hyperthermia and Actinomycin D are characterized by individual patterns. Obviously, they are dependent on proliferative activity rather than upon the particular type of tumor. The use of supranormal temperatures for the treatment of malignant tumors in man, also in combination with radiation or cytostatic drugs, is a possible and promising method of therapy. (Author abstract) (38 Refs)

7. FAILURE OF RNA SYNTHESIS TO RECOVER AFTER ULTRAVIOLET IRRADIATION: AN EARLY DEFECT IN CELLS FROM INDIVIDUALS WITH COCKAYNE'S SYNDROME AND XERODERMA PIGMENTOSUM.

Mayne LV, Lehmann AR
(c/o Lehmann) MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England
Cancer Res; 42(4):1473-1478 1982

Previous work has shown that in cells from the UV-sensitive genetic disorder, Cockayne's syndrome, DNA synthesis fails to recover after UV irradiation, despite the fact that these cells have no detectable defect in either excision or daughter-strand repair pathways. We now show that Cockayne cells, as well as cells from a number of patients with xeroderma pigmentosum, are sensitive to the lethal effects of UV irradiation in stationary phase under conditions in which no DNA is synthesized after irradiation. Furthermore, in normal and defective human fibroblasts, RNA synthesis is depressed after UV irradiation. In normal (dividing) cells, RNA synthesis recovers very rapidly, but this recovery does not occur in Cockayne cells, and it is reduced or absent in xeroderma pigmentosum cells from different complementation groups. Qualitatively, similar results are obtained with cells in stationary phase. The recovery of RNA synthesis in the various defective cell strains is not correlated with the overall extent of excision repair, but there is some correlation between recovery of RNA synthesis and cell survival after UV irradiation. These results implicate recovery of RNA synthesis as an important early response to UV irradiation. (Author abstract) (33 Refs)

8. RIBOSOMAL RNA TRANSCRIPTION IN VITRO IS SPECIES SPECIFIC.

Grummt I, Roth E, Paule MR
Institut fur Biochemie der Universitat Wurzburg, Rontgenring 11, D-8700 Wurzburg, W. Germany
Nature; 296(5853):173-174 1982

Previous studies have shown that specific transcription of ribosomal (r)DNA from mouse requires transcription factors from mouse cells; factors from heterologous sources did not support selective transcription. Studies are presented that show that in vitro transcription of rDNA isolated from mouse, a human source (HeLa cells), and a protozoan (Acanthamoeba), required completely homologous components. None of the three active cell-free systems was capable of correct initiation on the nonhomologous templates. A mixing experiment revealed a pronounced template selectivity by the transcription factors for RNA polymerases present in the crude extracts. If both human and mouse rDNA were present in the assay, the source of S-100 determined which template was transcribed. Results indicate that the cell-free transcription systems consisting of homologous RNA polymerase I and transcription factor(s) supplied by the S-100 extracts are only able to initiate correctly at homologous promoter sequences. Supplementation of mouse extracts with purified protozoan RNA polymerase I failed to result in specific transcription of the protozoan rDNA, suggesting the the species specificity of pre-ribosomal RNA synthesis resides, in part, in the transcription factors. (25 Refs)

9. TRANSCRIPTIONAL CONTROL OF THE EXPRESSION OF MOUSE GLOBIN GENES IN MYELOMA X ERYTHROLEUKEMIA CELL HYBRIDS.

Ar-Rushdi A, Tan KB, Croce CM
The Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Somatic Cell Genet; 8(2):151-161 1982

Hybrids were generated from fusion of thymidine kinase deficient Friend cells inducible for Hb production (line 745) with immunoglobulin-producing hypoxanthine-guanine phosphoribosyltransferase-deficient myeloma cells (line P3x63 Ag8). No Hb production was detectable in the hybrids by benzidine staining; subclones also lacked Hb. All the hybrids resembled the myeloma parental cell line in mode of growth: they were semidetached and composed of single or clustered suspension cells and cells that attached to the surface of the culture dishes. All of the hybrids and subclones assayed for IgG production secreted Ig-gammal heavy chain and kappa light chain. A 16 Svedberg (S) precursor RNA was detected in the nuclear extract and a 9 S RNA was found in both nuclear and cytoplasmic fractions of the Friend cells; however, no trace of globin messenger RNA or its precursor was found in the hybrids. The lack of Hb production in the hybrids was attributed to the absence of detectable transcripts of the globin gene(s). These results are compared with those previously reported from similar fusions. (26 Refs)

STUDIES OF HETEROGENEOUS NUCLEAR RNA

10. REGULATION OF DIHYDROFOLATE REDUCTASE GENE TRANSCRIPTION IN METHOTREXATE-RESISTANT MOUSE FIBROBLASTS.

Wu JS, Johnson LF
(c/o Johnson) Dept. Biochemistry, Ohio State Univ., Columbus, OH, 43210
J Cell Physiol; 110(2):183-189 1982

DNA-excess filter hybridization was used to study the rate of synthesis of dihydrofolate reductase (DHFR) heterogeneous nuclear (hn)RNA in serum-stimulated M50L3 cells, a methotrexate-resistant mouse 3T6 cell line. The rate of synthesis of DHFR hnRNA relative to total hnRNA varied over a considerable range when resting M50L3 cells were induced to reenter the cell cycle. The percentage of total hnRNA synthesized during a 20-min labeling period that hybridized to DHFR complementary (c)DNA was about 0.02-0.03% in resting M50L3 cells. When resting cells were serum stimulated to reenter the cell cycle, the percentage decreased initially to approx 0.01%, then began increasing about 6 hr following stimulation, and reached a max of approx 0.08% by approx 15 hr after stimulation. The relative rate of DHFR hnRNA synthesis began increasing at approx the same time (6 hr) and increased to approx the same extent by 15 hr following stimulation (3-4-fold) as does the relative rate of cytoplasmic DHFR mRNA. It was suggested that changes in the relative rate are primarily due to changes in the transcription of the DHFR gene. However, it is possible that the rate of synthesis of DHFR hnRNA remains relatively constant but that changes in the rate of synthesis of total hnRNA are responsible for alterations in the relative rate of DHFR hnRNA synthesis. The intracellular signals responsible for controlling DHFR gene expression are not known. High intracellular cyclic AMP was able to suppress DHFR gene transcription even when progression through the cell cycle was not blocked. The relationship of DHFR gene transcription to entry into the S phase was examined. (19 Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

11. POLYSOMAL POLYADENYLATED RNA AND ALBUMIN MESSENGER RNA IN MASTOMYS LIVER AND IN A CHEMICALLY INDUCED HEPATOCELLULAR CARCINOMA.

Krieg L, Krause-Leipholdt D, Wayss K, Volm M
Institut fur Experimentelle Pathologie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld, D-6900 Heidelberg, W. Germany
Cancer Res; 42(5):1986-1993 1982

A hepatocellular carcinoma line (H78) was established from a primary liver tumor induced in Mastomys natalensis by a single administration of dimethylnitrosamine. Six to 8 mo after transplantation (passages 5 to 7), well-differentiated tumors, still containing glycogen-storing cells, were isolated and used for the preparation of RNA. Polysomal polyadenylated RNAs from Mastomys liver and from the H78 tumor line were then compared by hybridization kinetics. Total kinetic complexities were 6.6 x 10(9) and 6.3 x 10(9) daltons for liver and tumor, respectively. Complexities of the high and middle abundant class were reduced in the hepatoma. Heterologous hybridization reactions revealed that, in terms of RNA mass, all or most of the polysomal polyadenylated RNA present in the liver was also present in the tumor and vice versa. However, shifts in the relative abundance of messenger RNA sequences were detected. In contrast to most other transplanted hepatomas, H78 has approx the same content of albumin messenger RNA on its polysomes as has untreated liver. (Author abstract) (44 Refs)

12. SPECIFIC PROTEIN SYNTHESIS REGULATED BY ESTROGEN IN HUMAN BREAST CANCER.

Edwards DP, Adams DJ, McGuire WL
(c/o McGuire) Dept. Medicine, Univ. Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX, 78284
J Steroid Biochem; 15:247-259 1981

Specific protein synthesis regulated by estrogen was studied in MCF-7 human breast cancer cells. Results for effects of estradiol on the pattern in protein synthesis, specificity of antiestrogen pretreatment, time course, estrogen dose response and hormone specificity of 24,000 mol wt (24k) stimulation, relationship between nuclear estrogen receptors and 24k stimulation, identity of 24k protein, two-dimensional electrophoresis, and estradiol stimulation of specific messenger RNA activity, are presented. Results indicate that specific proteins stimulated by estrogen in MCF-7 cells may prove to be suitable markers to study whether estrogens regulate expression of specific genes in breast cancer cells. (43 Refs)

13. PRIMARY STRUCTURE OF THE HUMAN MET- AND LEU-ENKEPHALIN PRECURSOR AND ITS MRNA.

Comb M, Seeburg PH, Adelman J, Eiden L, Herbert E
Univ. Oregon, Eugene, OR, 97403
Nature; 295(5851):663-666 1982

The nucleotide sequence of a complete cDNA copy of enkephalin precursor mRNA from human pheochromocytoma is reported. The corresponding amino acid sequence shows that the precursor is 267 amino acids long and contains six interspersed Met-enkephalin sequences and one Leu-enkephalin sequence. Five of the seven enkephalins are flanked on both sides by pairs of basic amino acid residues. The precursor does not contain the sequences of the opioid peptides, dynorphin, alpha-neo-endorphin or beta-endorphin. (Author abstract) (29 Refs)

14. MOUSE KIDNEY NONPOLYSOMAL MESSENGER RIBONUCLEIC ACID: METABOLISM, CODING FUNCTION, AND TRANSLATIONAL ACTIVITY.

Ouellette AJ, Ordahl CP, Van Ness J, Malt RA
Surgical Services, Shriners Burns Inst., Massachusetts General Hosp., Boston, MA
Biochemistry; 21(6):1169-1177 1982

To elucidate the distribution and function of mRNA in mouse kidney cytoplasm, we compared mRNA isolated from polysomal (greater than 80S) and native postpolysomal (20-80S) ribonucleoproteins with respect to synthesis and lifetime, sequence content, and translational activity. The 20-25% of cytoplasmic mRNA recovered from postpolysomal ribonucleoprotein is similar to polysomal mRNA in size (20-22S), in apparent half-life (1-13 hr), in major products of cell-free translation, and in nucleotide complexity (approx 4 x 10(7) nucleotides). The labeling kinetics of polysomal and postpolysomal mRNA suggest these mRNA populations are in equilibrium. [3H]cDNAs transcribed from polysomal and from postpolysomal poly(A)-containing mRNAs react with template mRNA and with the heterologous mRNA at the same rate (C0t1/2 approx 6.3 mol-s/L) and to the same extent (95%). Therefore, these mRNAs are equally diverse and homologous and occur at similar relative frequencies. Postpolysomal mRNA directs cell-free protein synthesis at only approx 30% of the rate of polysomal mRNA and to only 30% of the extent of mRNA from polysomes. Postpolysomal mRNA is approx three-fold less sensitive than polysomal mRNA to inhibition of translation by m7GMP, suggesting postpolysomal mRNA contains a greater fraction of molecules deficient in 5'-terminal caps. Postpolysomal mRNA may derive from renal mRNAs that initiate translation inefficiently and thus accumulate as postpolysomal ribonucleoproteins. (Author abstract) (44 Refs)

15. REPRESSION OF THE ALBUMIN GENE IN NOVIKOFF HEPATOMA CELLS.

Capetanaki YG, Flytzanis CN, Alonso A
Div. Biology, California Inst. Technology, Pasadena, CA, 91125
Mol Cell Biol; 2(3):258-266 1982

Immunoprecipitation of in vitro translation products of normal rat liver and Novikoff hepatoma messenger (m)RNA in a reticulocyte system with polysomal polyadenosine-containing RNAs revealed no detectable synthesis of albumin by the Novikoff cells. An albumin recombinant plasmid pBR322 was obtained by screening a rat liver complementary (c)DNA library with albumin (32P) cDNA reverse transcribed from immunoprecipitated mRNA. Restriction site mapping and translation arrest experiments were used to show the presence of the albumin-specific gene insert. Titration experiments using cDNA cloned to pBR322 plasmid probe demonstrated the absence albumin-specific sequences in both polysomal and nuclear polyadenylated and total RNA from Novikoff cells. RNA blotting on nitrocellulose paper with nick-translated albumin insert showed no albumin-specific sequence in the nucleus or in total RNA of Novikoff cells. Southern blotting of normal rat liver and Novikoff hepatoma genomic DNA using cloned albumin cDNA probe suggested no alteration in the albumin gene structure. The loss of the capacity to synthesize albumin by Novikoff cells apparently resulted from the absence of corresponding functional mRNAs, and translation control was evidently not a factor in control of expression of the genes for albumin. (39 Refs)

16. DISTRIBUTION AND SPECIFICITY OF SEQUENCES IN POLYADENYLATED NUCLEAR RNA OF NORMAL, REGENERATING, AND NEOPLASTIC LIVER.

Fausto N, Schultz-Ellison G, Atryzek V, Goyette M
Div. Biology and Medicine, Brown Univ., Providence, RI, 02912
J Biol Chem; 257(5):2200-2206 1982

We determined the homology between nuclear RNA of normal liver and that of regenerating and neoplastic livers. Because of the very low representation of the rare class of sequences (1 copy per cell or less) in liver nuclear RNA, very high RNA/cDNA ratios (as high as 1 x 10(5)) were generally necessary to obtain maximal levels of hybridization. Complementary DNA prepared from 16-hr regenerat ing liver polyadenylated nuclear RNA hybridized to the same extent with its homologous RNA and with polyadenylated nuclear RNA isolated from normal liver. We prepared, through several cycles of hybridization, a cDNA probe enriched for regenerating liver polyadenylated nuclear RNA sequences. Hybridization reactions with this enriched probe demonstrated marked differences in the abundance of classes of transcripts between nuclear RNA of normal and regenerating liver. However, the data do not support the view that there is a group of nuclear RNA sequences which is present in regenerating but not in normal liver. Hybridization reactions with cDNA prepared from livers with primary tumors indicated that polyadenylated nuclear RNA from those livers differs markedly from normal liver nuclear RNA in the distribution of its sequences. We conclude that the changes in the rare sequences of polyadenylated nuclear RNA during liver regeneration result from alterations in the abundance of some RNA sequences which are present in normal liver. The same conclusion applies to nuclear RNA of livers with primary tumors but in this case it was not possible to exclude the possibility that 'tumor-specific' nuclear RNA sequences might exist. (Author abstract) (32 Refs)

17. HORMONAL INDUCTION OF CASEIN GENE EXPRESSION LIMITED TO A SMALL SUBPOPULATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMOR CELLS.

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Cancer Res; 42(4):1355-1360 1982

In the hormonally responsive 7,12-dimethylbenz(a)anthracene (DMBA)- or N-nitrosomethylurea (NMU)-induced mammary carcinomas, regulatory mechanisms have been altered such that these tumors retain their hormonal dependence for growth but possess only a limited ability to synthesize the mammary gland-specific milk proteins. Quantitation of casein mRNA levels revealed that very low levels of casein messenger RNA (mRNA) were expressed in both the DMBA- and NMU-induced tumors growing in virgin animals (0.1 to 0.4% of the maximally induced 8-day-lactating mammary gland). Growth of DMBA-induced tumors in pregnant rats and the treatment of NMU-induced tumor-bearing animals with thioproperazine indicated that the tumor casein mRNA levels were hormone inducible (3.4-and 2.1-fold for the DMBA- and NMU-induced tumors, respectively). However, casein mRNA levels were still only 1 to 2% of those found in the normal mammary gland under the same hormonal environment. Localization of the casein-synthesizing cells in the DMBA-induced tumors by peroxidase-antiperoxidase staining and a specific casein antiserum indicated that, in both control and hormone-treated tumors, the vast majority of cells (greater than 95%) were unable to synthesize casein. The hormonal induction of casein mRNA sequences could be correlated with an increase in the number of cells synthesizing casein, which appeared as small clusters of cells throughout the tumors. Therefore, the loss of hormone-regulated differentiated function in these tumors, which maintained hormone-dependent growth, suggests the presence of a defective regulatory mechanism beyond the level of the hormone-receptor complex. (Author abstract) (29 Refs)

18. ABSENCE OF SIGNIFICANT H-2 AND BETA2-MICROGLOBULIN MRNA EXPRESSION BY MOUSE EMBRYONAL CARCINOMA CELLS.

Morello D, Daniel F, Baldacci P, Cayre Y, Gachelin G, Kourilsky P
Unite de Biologie Moleculaire du Gene, ER CNRS 201, SC INSERM 20, Institut Pasteur, 75724 Paris Cedex 15, France
Nature; 296(5854):260-262 1982

H-2 antigens and beta2-microglobulin (B2m) were used as probes to screen total polyadenylic acid [poly(A)]+ RNAs from various cell types. Trace amounts of poly(A)+ RNA from embryonal carcinoma cells were found to hybridize with these probes, a finding which contrasts with results obtained on poly(A)+ RNA prepared from differentiated cells. These results, together with the absence of major rearrangements in H-2 and B2m genes during differentiation, suggest that H-2 and B2m expression is probably controlled at the level of transcription. (32 Refs)

19. CORRELATION BETWEEN D REGION STRUCTURE AND ANTIGEN-BINDING SPECIFICITY: EVIDENCES FROM THE COMPARISON OF CLOSELY RELATED IMMUNOGLOBULIN VH SEQUENCES.

Auffray C, Sikorav JL, Ollo R, Rougeon F
Unite de Genetique et Biochimie de Developpement, E.R.A. CNRS 851, Institut Pasteur, 75724 Paris Cedex 15, France
Ann Immunol (Paris); 132(1):77-88 1981

Complementary DNA (cDNA) clones containing VH sequences of three myeloma proteins, of which two (UPC10 and ABE48) bind 2,6-levan, and one (MOPC173) has an unknown specificity, were constructed and sequenced. cDNA clones were compared to four sequences of anti-galactan myeloma proteins belonging to NIH BALB/c plasmacytoma. Starting with partially purified alpha heavy chain messenger RNA (mRNA) from ABE48 myeloma and gamma2a heavy chain mRNA from MOPC173 myeloma, collections of recombinant plasmids were constructed. Plasmids palpha48-16 and pG2a-173-27, which carry the most important part of the corresponding VH sequences were isolated using 650-base pair PstI fragment of pG2a-10-21 containing the VH sequence. Nucleotide sequences are presented. As a result of the cloning procedure, the sequence corresponding to the 5' end of the mRNA is not present in pG2a-173-27, which begins at the codon 5 of the variable region of the heavy chian (VH region), and in palpha48-16, which begins at codon 32 of the VH region. The amino-acid sequences presented were derived from the nucleotide sequences. The MOPC173 sequence agrees with a previously reported except for the exchange Asn/Asp at codons 52-54 and 73-74. Results confirm the strong correlation existing between D-region structure and antigen-binding specificity. (29 Refs)

20. DIFFERENT MRNAS FROM THE TRANSFORMING REGION OF HIGHLY ONCOGENIC AND NON-ONCOGENIC HUMAN ADENOVIRUSES.

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Nature; 295(5851):705-707 1982

Messenger RNA (mRNA) produced from the transforming region of DNA from human adenoviruses was characterized. Adenoviruses were cultured by infection of A549 cells derived from human oat-cell carcinoma. RNA was labeled with 32P. Complementary DNA (cDNA) was prepared from viral mRNA and hybridized to restriction enzyme fragments of viral DNA. The transforming region of viral DNA was characterized by inserting cDNA into pBR322 plasmids and hybridizing to labeled DNA fragments. Characterization of 38 clones containing sequences from the E1B region of the highly oncogenic Ad12 adenovirus showed three classes of mRNA. Ad12 mRNA were compared with mRNA from weakly (Ad5 and Ad7) and non-oncogenic (Ad2) adenoviruses. Results identified two donor sites, designated D1 and D2, and three acceptor sites, designated A1, A2, and A3, in the three classes of mRNA. Donor site D1 was well-conserved and generated a large splice in Ad12 and Ad5. Site D2 was well-conserved and generated a small splice in Ad5, Ad7, and Ad12. Site A1 generated a middle splice in Ad12 not found in Ad5. Site A2 was found in all three viral serotypes. Site A3 was found only in Ad7 and Ad12. Results indicate that mRNA from Ad12 have different structures from mRNA from Ad2, but suggest that the adenoviruses have evolved together. (30 Refs)

21. VIRAL GENE PRODUCTS IN ADENOVIRUS TYPE 2-TRANSFORMED HAMSTER CELLS.

Esche H
Inst. Genetics, Univ. Cologne, Cologne, W. Germany
J Virol; 41(3):1076-1082 1982

I have analyzed viral gene products expressed in five adenovirus Type 2 (Ad2)-transformed hamster embryo cell lines (Ad2 HE1-5) by cell-free translation of cytoplasmic, viral RNA which was selected by hybridization to cloned restriction endonuclease fragments of Ad2 DNA. Proteins synthesized in vitro were analyzed by electrophoresis in sodium dodecyl sulfate-polyacrylamide gels and compared with those directed by RNAs prepared from productively infected cells. The early regions E1 and E4 of adenovirus Type 2 (Ad2) were found to be expressed in all of five Ad2-transformed hamster embryo cell lines. RNA transcribed from early region E2, which codes for the 72,000-mol-wt (72K) DNA-binding protein was detected in cell line HE1 only, and early region E3 was expressed exclusively in cell line HE4. RNA transcribed from the region between approx 12 and 35 map units, coding for immediate early (13.5K, 52/53K) and intermediate early proteins (13.6K, 16K, 17K, 87K), as well as RNA from late genes, was not found in any of the cell lines. The proteins synthesized in vitro by RNA prepared from cell lines HE1 to HE5 had electrophoretic mobilities similar to those programmed by RNA from productively infected cells. (Author abstract) (23 Refs)

22. SYSTEMATIC ALTERATION OF THE NUCLEOTIDE SEQUENCE PRECEDING THE TRANSLATION INITIATION CODON AND THE EFFECTS ON BACTERIAL EXPRESSION OF THE CLONED SV40 SMALL-T ANTIGEN GENE.

Gheysen D, Iserentant D, Derom C, Fiers W
Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat 35, B-9000 Ghent, Belgium
Gene; 17(1):55-63 1982

In a series of recombinant plasmids which contain the simian virus 40 small-t antigen gene under control of the thermoinducible pL promoter of phage lambda, a Shine-Dalgarno ribosome-recognition (SD) sequence was created at various distances in front of the small-t translation initiation codon. In some other constructions the distance between the initiating AUG and the SD sequence was conserved while the intervening nucleotides were changed. Effects of these variables on production levels of the 19,000-dalton full-size small-t protein and on the 14,500-dalton small-t-related species are explained in terms of messenger RNA secondary structure models that could be drawn for different plasmids. (19 Refs)

23. CONSTRUCTION AND CHARACTERIZATION OF SV40 RECOMBINANTS WITH BETA-GLOBIN CDNA SUBSTITUTIONS IN THEIR EARLY REGIONS.

Southern PJ, Howard BH, Berg P
(c/o Berg) Dept. Biochemistry, Stanford Univ. Medical Center, Stanford, CA, 94305
J Mol Appl Genet; 1(3):177-190 1981

A complementary DNA (cDNA) segment coding for rabbit beta-globin (RBG) was inserted at three different sites in the early region of simian virus 40 (SV40). Monkey kidney cells infected with each hybrid SV40 genome produced stable, spliced polyadenylated messenger RNA (mRNA) containing the RBG cDNA sequence. Only the hybrid mRNAs containing the RBG coding sequences immediately proximal to the 5' end of the mRNA underwent translation to produce RBG. The recombinants containing the RBG coding sequence towards the 3' end of the early region yielded small t antigen and abbreviated forms of large T antigen, but little or no detectable RBG. The results suggested that the position of the RBG cDNA segment in the early region of SV40 influences the translation of the transduced coding sequences. (41 Refs)

24. MECHANISM OF INTERFERON ACTION. DIFFERENTIAL EFFECT OF INTERFERON ON THE SYNTHESIS OF SIMIAN VIRUS 40 AND REOVIRUS POLYPEPTIDES IN MONKEY KIDNEY CELLS.

Daher KA, Samuel CE
(c/o Samuel) Section Biochemistry and Molecular Biology, Univ. California, Santa Barbara, CA, 93106
Virology; 117(2):379-390 1982

The effect of interferon (IFN) treatment on the synthesis of viral proteins was examined in BSC-1 monkey kidney cells singly and doubly infected with simian virus 40 (SV40) and reovirus. The pattern and amount of SV40 T antigen and reovirus lambda, mu, and sigma polypeptide synthesis was comparable in singly and doubly infected cells in the absence of IFN treatment. As determined by Yakobson et al and Kingman and Samuel SV40-specific RNA synthesis is inhibited by treatment of cells with IFN before infection, but is not inhibited by IFN treatment after infection. IFN treatment initiated before infection inhibited the synthesis of both SV40 T antigen and reovirus polypeptides. However, SV40 T antigen synthesis was not inhibited in SV40 wt or tsA mutant-infected cells when treated with monkey kidney or human leukocyte IFN after infection. By contrast, reovirus polypeptide synthesis was markedly inhibited in BSC-1 cells treated with IFN after SV40 infection and superinfected with reovirus. SV40 infection did not rescue reovirus polypeptide synthesis from the inhibitory action of IFN, and reovirus infection did not alter the resistance of SV40 T antigen synthesis to IFN in cells IFN-treated after SV40 infection. Total cellular protein synthesis was not significantly affected by IFN treatment. These results suggest that the interferon-induced inhibitor(s) of protein synthesis discriminate between SV40 and reovirus mRNAs; the translation of SV40 mRNA, like most cellular mRNAs, is not affected under conditions where the IFN-induced inhibitor(s) significantly affect the translation of reovirus mRNA. (Author abstract) (40 Refs)

25. TRANSCRIPTS OF CELLULAR ANALOG OF VIRUS SARCOMA SRC GENE IN MOUSE LIVER.

Mett VL, Chumakov IM, Kiselev LL
Inst. Molecular Biology, Moscow, USSR
Dokl Akad Nauk SSSR; 261(6):1471-1472 1981

Analysis of the expression of protosarc gene in the liver of mice uninfected with Moloney sarcoma virus (MSV) showed synthesis of poly(A)-RNA homologous to RNA of MSV. Poly(A)-RNA showing hybridization with src gene of MSV were also detected in the liver of mice treated with the hepatocarcinogen o-aminoazotoluene. These findings can indicate transcription of the endogenous sarcoma provirus during chemical carcinogenesis. (7 Refs) (In RUS)

26. PARTICIPATION OF SUBGENOMIC RETROVIRAL MRNAS IN RECOMBINATION.

Wang LH, Stacey DW
Rockefeller Univ., New York, NY, 10021
J Virol; 41(3):919-930 1982

Envelope glycoprotein (env) mRNA from avian retroviruses was injected into cells transformed by env-deleted Bryan Rous sarcoma virus [RSV(-)]. The genetic deficiency of RSV(-) was complemented, and infectious transforming virus was released for many days after these injections. The long-term activity of the injected env mRNA is believed to be due to reverse transcription of the injected RNA after its incorporation into virus particles. The resulting subgenomic provirus, presumed to be integrated in to host DNA, is able to direct the continuous synthesis of additional env mRNA. In some of these cultures, replication-competent viruses appeared many days after injection. The analysis by RNase T1 oligonucleotide fingerprinting showed that the RNA of these virus genomes contained oligonucleotides characteristic of both RSV(-) and the env mRNA injected. In all viruses analyzed the 5' two-thirds and a 3' terminus of the genome were derived from RSV(-) and the env gene from the injected mRNA. Our results thus strongly indicate that these viruses were generated via recombination between RSV(-) and env mRNA. The demonstration of involvement of an MRNA sequence in recombination may be of importance in the divergence of retroviruses and in the mechanism of interaction between retroviruses and host nucleotide sequences. (Author abstract) (32 Refs)

27. EXPRESSION OF THE PRC II AVIAN SARCOMA VIRUS GENOME.

Adkins B, Hunter T, Beemon K
Institut fur Virusforschung, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
J Virol; 41(3):767-780 1982

We found that the genomic RNA of the replication-defective avian sarcoma virus PRC II was 4.0 kilobases long. A Northern blot analysis of the viral RNAs present in PRC II-transformed cells showed that the PRC II genome was expressed as a single 4.0 kilobase mRNA species. In vitro translation of poly-adenylic acid-containing 70S virion RNA yielded two highly related proteins of 110,000 and 105,000 daltons (P110 and P105), which were synthesized from messenger activity that sedimented as expected for the 4.0 kilobase PRC II genome (at 25 to 27S). P110 and P105 were identified as in vitro translation products of the PRC II genome by immunoprecipitation and tryptic peptide mapping and were the only PRC II-specific polypeptides detected by in vitro synthesis. In addition, we found that immune complexes prepared from PRC II 70S virion RNA in vitro translation products contained a tyrosine-specific protein kinase activity. A comparison of the in vitro- and in vivo-synthesized proteins revealed that PRC II-transformed cells also contained 110,000- and 105,000-dalton proteins, which were indistinguishable from in vitro-synthesized P110 and P105 by electrophoretic mobility and tryptic peptide analysis. Both P110 and P105 were present in producer cells and in seven individual nonproducer clones. A pulse-chase analysis showed that P105 was the primary translation product of the PRC II genome and that P110 was derived from P105 by post-translational modification. Under conditions of long-term labeling with [35S]methionine, P110 and P105 were present in a molar ratio of approximately 1:1. These results indicated that the transformation-specific product of the PRC II genome, previously referred to as a single component (P105), actually consists of two polypeptides related by post-translational modification. (Author abstract) (36 Refs)

28. HUMAN NUCLEOTIDE SEQUENCES RELATED TO THE TRANSFORMING GENE OF A MURINE SARCOMA VIRUS: STUDIES WITH CLONED VIRAL AND CELLULAR DNAS.

Chumakov IM, Zaharovsky ER, Prassolov VS, Mett VL, Kisselev LL

Inst. Molecular Biology, USSR Acad. Sciences, ul. Vavilova 32, Moscow V-334, USSR

Gene; 17(1):19-26 1982

Fragments of the human genome related to onc-gene of Moloney sarcoma virus (MSV), mos-specific, and Moloney leukemia virus (MLV)-specific nucleotide sequences were cloned. An attempt was made to visualize the expression of oncogenes by the Northern blotting technique, using a mos-specific probe, and preliminary data are presented. MSV clone 124 was isolated from tissue culture supernatant obtained from chronically infected TB cells. A total of 3 x 10(5) recombinant phages containing human DNA insert were subjected to screening. [32P]Complimentary (c)DNA-MSV was used as a probe and 30 labeled plaques were obtained. All of them were tested with the mos-specific probe, but with one exception, no mos-specific DNA was detected. After the whole screening procedure, 19 recombinant phages with inserts hybridizable with the mos-specific probe were selected. Clones isolated with various probes could be subdivided into those that contain MLV-related sequences and lack mos-related sequences and those that contain both types of sequences. The hybridization pattern of polyadenylic+RNA from normal mouse liver with [32P]cDNA-MSV is presented. Several fractions were revealed which hybridize also with cDNA-MLV. These RNA appeared to be transcripts of endogenous proretroviruses homologous to MLV which probably are present in mouse liver. When a mos-specific probe was used, no hybridization was detected with RNA isolated independently from several groups of mice. (32 Refs)

STRUCTURE AND LEVELS OF RIBOSOMAL RNA

29. SENSITIVITY TO RNASE TREATMENT OF RIBOSOMES AND RRNA FROM NORMAL RAT LIVER AND NOVIKOFF HEPATOMA.

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Br J Cancer; 45(1):140-143 1982

Biochemical assays were used to verify whether fresh ribosomes isolated from Novikoff hepatomas differ from those of normal Wistar rat liver in sensitivity to RNase and capacity to bind basic dyes. Ribosomal RNA (rRNA) was extracted from normal and tumor ribosomes by the dodecyl sulfate-phenol method. The amounts of RNA hydrolyzed by RNase were expressed as the percentage of total RNA (determined by complete hydrolysis of 5 absorbance units of ribosome suspension or rRNA soln after incubation with 5 ml 10% perchloric acid for 1 hr at 25 C) Nearly max hydrolysis was observed in both normal and tumor preparations after 1 hr treatment. Tumor ribosomes incubated with RNase at a final concentration of 20 nanog/ml showed a linear rate of RNA degradation to 6% and 8% after 20 and 30 min, respectively. The same treatment had little effect on ribosomes from normal liver; RNase concentration had to be increased 10-fold to obtain the rates of hydrolysis seen with tumor ribosomes. The ribosomes from tumor preparations were approx 5x as sensitive to pancreatic RNase treatment as those of normal livers. Basic changes occurring in the liver ribosome as a result of neoplastic transformation may be responsible for both the increased dye-binding of tumor ribosomes and the greater sensitivity to RNase. (13 Refs)

30. INHIBITORY EFFECTS OF METHYL GLYOXAL ON DNA, RNA AND PROTEIN SYNTHESIS IN CULTURED GUINEA PIG KERATOCYTES.

White JS, Rees KR

Dept. Biochemical Pathology, Sch. Medicine, Univ. Coll. London, University St., London WC1F 6JJ, England

Chem Biol Interact; 38(3):339-347 1982

The inhibitory action of methyl glyoxal upon protein, RNA and DNA synthesis in guinea pig keratocytes has been investigated. Methyl glyoxal directly inhibits each of these processes. Inhibition of protein synthesis results from an action upon initiation of translation. Methyl glyoxal induces polysome degradation which is prevented by pretreatment with cycloheximide. Further analysis of translation indicates that elongation and termination are not affected. Inhibition of ribosomal RNA synthesis results from inhibition of maturation. Methyl glyoxal was found to inhibit the appearance of 28S rRNA in the cytoplasm from pulse-labeled precursors. The significance of these results is discussed in relation to cell injury by ketals. (Author abstract) (21 Refs)

STRUCTURE AND LEVELS OF TRANSFER RNA

31. A SYSTEM FOR MEASURING THE FREQUENCIES OF TANDEM AND NON-TANDEM DOUBLE BASE SUBSTITUTIONS INDUCED BY ULTRAVIOLET IRRADIATION.

Dunst RW, Coleman RD, Harnish BW, Hill CW
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MGG; 184(3):445-449 1981

A system based on missense suppressor mutations affecting an Escherichia coli glycine tRNA was used for measuring the relative frequencies of a single base substitution, a tandem double base substitution and a non-tandem double base substitution all occurring in the same triplet and in the same mutagenic treatment. RNA sequencing studies reported here have shown that the glyUsuGAA mutation results from a CCC-TTC tandem double substitution n the anticodon region of the gene coding for tRNAGly/GGG. Following mutagenesis the culture is induced for phage production and the resulting lysate assayed for phage carrying any one of the three suppressor alleles. An important feature of the system is that it circumvents the problem of distinguishing the rare double mutations from the more abundant background. We have found that with doses of UV irradiation sufficient to reduce the viable cell count 98-99%, the tandem double base substitution occurs 0.01 as frequently as the single. The tandem double substitution occurs about 4x more frequently than the nontandem double substitution. The sequence studies utilized a recombinant plasmid bearing the glyUsuGAA allele inserted between the EcoRI and SalI sites of pBR313 as well as defective lambda transducing phage in order to amplify and selectively label the suppressor tRNA. Thus the mutant tRNA could be purified sufficiently to permit sequencing despite the fact that it is aminoacylated very poorly. It was found that the nature and extent of tRNA modification varied with the method of amplification. Namely, use of the plasmid for amplification resulted in variable levels of 2'-O-methyl-G at position 17, while use of the phage resulted in variable modification of a G in the anticodon stem. (12 Refs)

32. STUDIES ON THE FUNCTION OF THE NON-PRIMER TRNAS ASSOCIATED WITH THE 70S RNA OF AVIAN MYELOBLASTOSIS VIRUS.

Waters LC, Burke JR, Stulberg MP
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Biochim Biophys Acta; 696(2):201-207 1982

Significant amounts of three tRNAs are associated with the 70S RNA of avian myeloblastosis virus (AMV). The temperatures at which they are half dissociated from the 70S RNA in 50 mM NaCl and their respective quantities relative to 35S RNA are: tRNAArg, 51 C, 1.6; tRNALys, 57 C, 0.7 and tRNATrp, 76 C, 1.0. Possible functions for the non-primer tRNAs (tRNAArg and tRNALys) were evaluated by determining the effect of their thermal dissociation on: (a) conversion of 70S to 35S RNA, (b) capacity of 70S and/or 35S RNA to be translated in vitro, and (c) capacity of 70S and/or 35S RNA to be reverse transcribed in vitro. Conversion of 70S to 35S RNA occurred with a tm of 56 C and is consistent with the hypothesis that tRNALys might be involved in joining two 35S RNA subunits to form the 70S RNA complex. There was no indication that the association of either tRNAArg or tRNALys influenced the rate or quality of translation of 70S or 35S RNA. A decrease in the rate at which 70S RNA is transcribed occurs in parallel with the dissociation of tRNAArg and tRNALys. (Author abstract) (29 Refs)

33. BRAIN TRANSFER RNA. I. METHYLATION OF NEWLY SYNTHESIZED TRNA.

Chaudhary KD, Carrier-Malhotra L, Murthy MR
Departement de Biochimie, Faculte de Medecine, Universite Laval, Quebec G1K 7P4, Canada
Neurochem Res; 7(1):55-65 1982

Rat brain cerebral cortex and cerebellum incubated with labeled precursors showed different initial rates of synthesis and methylation of transfer RNA; however, over the course of the 5-hr study, the final degree of methylation was the same. Differences in the rates of incorporation of the radioactivities in both tissues can be explained by differences in rates of equilibrium of labeled precursors within the pools. (24 Refs)

34. BRAIN TRANSFER RNA. II. ANALYSIS OF MODIFIED NUCLEOSIDES.

Chaudhary KD, Carrier-Malhotra L, Murthy MR
Departement de Biochimie, Faculte de Medecine, Universite Laval, Quebec G1K 7P4, Canada
Neurochem Res; 7(1):67-77 1982

The tritium derivative technique was used to analyze nucleosides of transfer RNAs (tRNAs) from rat and calf brains. Fluorograms showed qualitative changes in minor nucleoside components. Cerebellar and cortical tRNAs showed no significant quantitative differences in methylated constituents. Two-dimensional polyacrylamide gel electrophoresis of brain transfer RNA showed qualitative and quantitative changes during postnatal development. (33 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

35. PURIFICATION AND CHARACTERIZATION OF NUCLEOLAR RIBONUCLEIC ACID METHYLASE FROM EHRLICH ASCITES TUMOR CELLS OF MICE.

Obara M, Hirano H, Higashi K
(c/o Higashi) Dept. Biochemistry, Sch. Medicine, Univ. Occupational and Environmental Health, Kitakyushu 807, Japan
Biochemistry; 21(6):1374-1380 1982

RNA methylases in the extracts of mouse tumor cells were separated on a (diethylaminoethyl)cellulose column in two distinct activities. It was further revealed that the methylase from the isolated nucleoli corresponded to the peak eluted with lower concentration of salt and the extranucleolar nuclear methylase to that with higher salt concentration. Isolation of nucleoli from the purified nuclei was found to be profitable to a 10x increase of specific activity of nucleolar methylase. The nucleolar methylase has been highly purified and characterized the properties of the enzyme. The purified nucleolar methylase was sedimented as a single component with a mol wt of 130,000 on a sucrose density gradient. This enzyme is optimally active at pH 7.5 and sensitive to N-ethylmaleimide. The presence of a thiol-protecting reagent such as beta-mercaptoethanol is necessary for its full activity. The enzyme required no divalent cations and its activity was suppressed in the presence of either 5 mM MnCl2 or 10 mM MgCl2. An apparent KM value for S-adenosyl-L-methionine and a KI value for S-adenosyl-L-homocysteine were 4 x 10(-7) M and 1.0 x 10(-6) M, respectively. Methyl-acceptance activities of homologous RNAs such as total cellular RNA, nucleolar RNA, and 45S ribosomal precursor RNA of Ehrlich tumor cells by nucleolar methylase from the same tumor cells were negligible, but heterologous RNA, prepared from Escherichia coli, served as a good substrate for the nucleolar methylase. On the other hand, hypomethylated RNA was prepared after th e treatment of tumor cells with cycloleucine, an inhibitor of S-adenosylmethionine formation. The methyl-acceptance activities of both hypomethylated 18S and 28S rRNA were significantly greater than that of hypomethylated tRNA. (Author abstract) (30 Refs)

36. PRESENCE OF 2',5'-OLIGO(A) AND OF ENZYMES THAT SYNTHESIZE, BIND, AND DEGRADE 2',5'-OLIGO(A) IN HELA CELL NUCLEI.

Nilsen TW, Wood DL, Baglioni C
Dept. Biological Sciences, Univ. New York at Albany, Albany, NY, 12222
J Biol Chem; 257(4):1602-1605 1982

Nuclei prepared from HeLa cells by lysis with nonionic detergents or by a nonaqueous fractionation procedure were assayed for enzymatic activities which synthesize, bind, and degrade 2',5'-oligo(A). Isolated nuclei synthesized micromolar concentrations of 2',5'-oligo(A) when incubated with poly(inosinic).poly(cytidylic) acid. The products of nuclear synthesis were identified with authentic 2',5'-oligo(A) by several criteria. The nuclei synthesized nanomolar amounts of 2',5'-oligo(A) even when incubated without added double-stranded RNA. These oligonucleotides were identified by their pattern of degradation with different nucleases and by a specific competition-binding assay. This assay revealed the presence in nuclei of an activity which binds 2',5'-oligo(A) with an affinity constant similar to that of the cytoplasmic binding activity previously identified with the 2',5'-oligo(A)-dependent endoribonuclease. The nuclei had also an activity which degraded 2',5'-oligo(A). Finally, unincubated nuclei isolated by the nonaqueous fractionation procedure contained detectable concentrations of 2',5'-oligo(A). These results show that an activator of the enzyme which synthesizes 2',5'-oligo(A) is present in nuclei and that these oligonucleotides are normally formed in HeLa cells, and suggest a possible role for the 2',5'-oligo(A)-activated endoribonuclease in nuclear RNA metabolism. (Author abstract) (25 Refs)

OTHER RELATED STUDIES

37. THE BACTERIAL RIBOSOME: A PROGRAMMED ENZYME.

Gassen HG
Institut fur Organische Chemie und Biochemie, Technische Hochschule, Petersenstrasse 22, D-6100 Darmstadt, W. Germany
Angew Chem [Engl]; 21(1):23-36 1982

An introduction to the steps involved in ribosome-dependent protein synthesis and to the structures of the compounds involved is presented. An attempt is made to elucidate the mechanistic principles of the ribosome as a programmed enzyme. Topics include ribosome-dependent protein biosynthesis; structure and function of the ribosomal machinery; transfer ribonucleic acids; messenger RNA, the program for the biosynthesis of proteins; proteins that function as enzymes, carriers, and modulators of transfer RNA conformation; selection of the beginning of a gene and framing the messenger RNA by formation of the initiation complex; and peptide chain elongation in protein biosynthesis. (89 Refs)

38. MODIFICATIONS OF CHROMATIN STRUCTURE IN CONTROL OF GENE EXPRESSION.

Hull LA
104 Depot St., New Sharon, IA, 50207
Med Hypotheses; 8(2):113-133 1982

The mechanisms controling gene expression and cellular differentiation in higher eukaryotic organisms are an active area of research in molecular biology. This article reviews what is known about chromatin structure and its regulations, and the following aspects are included the basic building block - the nucleosome,; the histone and nonhistone proteins which maintain chromosome structure and control transcription, the replication and transcription enzymes, repetitive sequences in DNA, DNA introns, and chromosomal RNA. A number of chromatin modifications such as DNA methylation and phosphorylation-dephosphorylation or acetylation-deacetylation of chromosomal proteins, and apparently involved in the control of gene expression are discussed. Tumor viruses and carcinogens may cause changes in chromatin structure resulting in a circumvention of normal cell cycle controls of proliferation. (68 Refs)

39. PROCESSED GENES: A DISPERSED HUMAN IMMUNOGLOBULIN GENE BEARING EVIDENCE OF RNA-TYPE PROCESSING.

Hollis GF, Hieter PA, McBride OW, Swan D, Leder P
Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, Bethesda, MD, 20205
Nature; 296(5855):321-325 1982

A dispersed immunoglobulin pseudogene carries two hallmarks of RNA processing - spliced J and C regions and a poly (A)-rich tail. Its discovery strengthens the notion that processed genes are a significant feature of the mammalian genome and that genetic information can return to the genome via an RNA intermediate. (Author abstract) (38 Refs)

40. DETECTION OF DOUBLE-STRANDED RNA IN ASCITIC FLUID OF ZAJDELA'S HEPATOMA.

Vinter VG, Alimova FK, Zotkina NL
V. I. Ul'ianov-Lenin State Univ., Kazan, USSR
Eksp Onkol; 4(1):28-32 1982

The results of isolation of RNA from the ascitic fluid of Zajdela's hepatoma are reported. Determination of the melting point, chromatographic fractionation on the column with hydroxyapatite cellulose, and interactions with RNAse indicated the double-stranded structure of RNA molecules. These findings explain the stability and relatively high content of RNA in the ascitic fluid. (19 Refs) (In RUS)

41. CHEMOTHERAPY OF GENITOURINARY TUMORS.

Yagoda A
Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cancer- Achievements, Challenges, and Prospects for the 1980s, Proceedings of an International Conference held in New York, 14-16 September, 1980. Vol. 2, Memorial Sloan-Kettering Cancer Center New York, NY. Burchenal, J. H. and Oettgen, H. F., eds. (New York, Grune and Stratton), 944 pp., 1981.

Cytotoxic and hormonal chemotherapy for adrenal, renal, bladder, prostate, and penile malignancies are reviewed. Trials of both individual agents and combinations of agents are described; a trial of immune RNA against adult kidney cancer is discussed. Efficacy of cytotoxic chemotherapy has been marginal for adrenal, renal, and prostate tumors but moderate for urinary bladder and penile malignancies. (58 Refs)

42. STABLE TRANSCRIPTION COMPLEXES OF XENOPUS 5S RNA GENES: A MEANS TO MAINTAIN THE DIFFERENTIATED STATE.

Bogenhagen DF, Wormington WM, Brown DD
Dept. Pharmacological Sciences, State Univ. New York, Stony Brook, NY, 11794
Cell; 28(2):413-421 1982

Cloned 5S RNA genes added to a Xenopus oocyte nuclear extract assemble into stable active transcription complexes that persist for many rounds of 5S RNA synthesis. This stability of the complex has been demonstrated by its resistance to dilution and to competitor DNA. A stable complex is formed within minutes and lasts for at least 40 rounds of transcription per template over several hours. Stable, transcriptionally inactive complexes can be formed by incubation of cloned 5S RNA genes in an oocyte nuclear extract depleted of a 5S-specific transcription factor and supplemented with histones. The stable, transcriptionally active and inactive states of 5S RNA gene complexes that can be formed in vitro are analogous to the states of the somatic and oocyte 5S RNA genes as they exist in somatic cell chromatin. Oocyte 5S RNA genes remain repressed in chromatin isolated from somatic cells, but can be activated by washing chromatin with high salt. Maintenance of the differentiated state of cell requires that selected genes remain stably active while others are stably repressed for long periods of time. We propose that stable transcription complexes may play an important role in the maintenance of the differentiated state in eucaryotic cells. (Author abstract) (28 Refs)

43. DELETIONS WITHIN THE TRANSFORMATION-SPECIFIC RNA SEQUENCES OF ACUTE LEUKEMIA VIRUS MC29 GIVE RISE TO PARTIALLY TRANSFORMATION-DEFECTIVE MUTANTS.

Bister K, Ramsay GM, Hayman MJ
Max-Planck-Institut fur Molekulare Genetik, D-1000 Berlin 33, W. Germany
J Virol; 41(3):754-766 1982

The viral RNAs of three nonconditional mutants of avian myelocytomatosis virus MC29 were analyzed. These mutants, which were originally isolated from the quail producer line Q10 and were designated 10A, 10C, and 10H, have lost most of the ability to transform hematopoietic cells in vitro and to induce tumors in vivo, but they still transform cultured fibroblasts with the same efficiency as wild-type (wt) MC29. Electrophoretic analyses showed that the mutant genomic RNAs were smaller than the 5.7-kilobase genome of wt MC29; the genomes of mutants 10A, 10C, and 10H were about 5.5, 5.3, and 5.1 kilo bases long, respectively. Analyses of the transformation-specific sequences of these mutant RNAs by a combination of T1 oligonucleotide fingerprinting and hybridization with cDNA from the transformation-specific sequences myc of wt MC29 or competition hybridization including wt MC29 RNA revealed that deletions of myc-specific sequences had occurred. The deletions in all three mutants overlapped, since they all had lost one particular myc-specific oligonucleotide. In agreement with the size of the genomic RNAs, mutants 10C and 10H had lost two additional myc oligonucleotides, and mutant 10A contained a modified myc oligonucleotide. The locations of the deletions were deduced from comparisons with previously established oligonucleotide maps of several members of the MC29 subgroup of acute leukemia viruses and by hybridization of wt and mutant RNAs to molecularly cloned subgenomic fragments of wt MC29 proviral DNA, representing the 5' and 3' domains of the myc sequence. We found that the deleted sequences represented overlapping internal segments of the myc sequence and that the borders of myc with the partial complements of the virion genes gag and env appeared to be conserved in mutant and wt MC29 RNAs. The correlation between the altered transforming potential for hematopoietic cells and the partial deletion of myc in the mutant RNAs provided direct genetic evidence for the involvement of myc in oncogenesis. However, the unaffected efficiency of these mutants in fibroblast transformation suggested that the deleted sequences are not essential for the fibroblast-transforming potential of the onc gene of MC29. (Author abstract) (31 Refs)

44. ISOLATION OF A KIRSTEN MURINE LEUKEMIA VIRUS MUTANT TEMPERATURE SENSITIVE FOR PARTICLE PRODUCTION AND ENV GENE MINUS.

Horwich A, Dickson C, Ozanne B
(c/o Ozanne) Dept. Microbiology, Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX, 75235
Virology; 118(1):136-147 1982

An NIH/3T3 cell, nonproductively infected with Kirsten murine leukemia virus (Ki-MLV), was isolated shortly after a low multiplicity of infection. The clone, K23, harbors a Ki-MLV genome with two defects: virus particle production is temperature sensitive and no envelope gene products can be detected immunologically. Intracellular Ki-MLV RNA consists of a single species which is of genome size. No Ki-MLV RNA is detected which corresponds to the env gene mRNA. This defect in RNA processing accounts for the lack of gp70 and p15E. The temperature-sensitive lesion may be in processing of Pr65gag or Pr65gag/pol precursor proteins. At 39 or 33 C the cells harbor Pr65gag and Pr180gag/pol. Intracellular p30, however, is only detected in cells at 33 C. At 33 C, the permissive temperature, virus particles are released which have a density of 1.13 g/ml, contain p30, p12, p10, reverse transcriptase, and RNA, but lack gp70 and p15E. A t 39 C no particles are detected. Thus, K23 appears to contain a viral genome with mutations which affect processing of both viral proteins and mRNAs. The nature of these defects is discussed. (Author abstract) (31 Refs)

45. CHARACTERIZATION OF THE RIBONUCLEIC ACID OF A TYPE D RETROVIRUS (PMFV) ISOLATED FROM A PERMANENT HUMAN CELL LINE.

Mothes E
Zentralinstitut fur Krebsforschung, Lindenberger Weg, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(3):191-197 1982

Similarities in size, subunit structure, and the presence of associated RNA of the major RNA species of permanent human fibroblasts virus (PMFV), Mason-Pfizer monkey virus (MPMV), and other retroviruses were studied. The virus was propagated in suspension culture of human rhabdomyosarcoma A204 cells. PMFV 3H-RNA was extracted from purified virus (peak fraction 1.14-1.18 g/ml) by the phenol-phase method. Comparison of the profiles showed that PMFV contains high-(60-70 Svedberg units; S) and low-mol wt (approx 7 S) components. RNA was isolated with the same method from the 1.20-1.23 g/ml peak fraction (virus core). A high mol wt species (60-70 S) was observed. Treatment with heat (65 C) resulted in a decrease of the sedimentation coefficient to approx 30 S. Best results were obtained with RNA from fresh virus isolated from cell sediments. Chromatographic profiles obtained with 60-70 S PMFV 3H-RNA and with 30 S PMFV 3H-RNA from whole virions of virus core are shown. Radioactivity bound to the column eluted mainly at 30-45 C. This corresponded to polyadenylic acid (poly A) regions of 80-300 adenylate residues. The presence and length of the poly A stretch of PMFV RNA, the size of native 60-70 S PMFV RNA and its dissociation by heat to subunit structures of approx 30 S showed the similarity to MPMV RNA. (14 Refs)

46. REVERSE TRANSCRIPTASE ASSOCIATED WITH AVIAN SARCOMA-LEUKOSIS VIRUSES. III. INFLUENCE OF PRIMER CHAIN LENGTH ON THE INITIATION OF DNA SYNTHESIS.

Fukui T, Ishihama A, Ohtsuka E, Ikehara M, Fukuda R
(c/o Ishihama) Inst. Virus Res., Kyoto Univ., Sakyo-ku, Kyoto, Kyoto 606, Japan
J Biochem (Tokyo); 91(1):331-339 1982

The influence of oligodeoxynucleotide chain length on the priming activity of the reverse transcription was investigated in poly(A)-dependent poly(dT), poly(C)-dependent poly(dG) and influenza virus RNA-dependent cDNA synthesis by the alpha-beta-form enzyme of the RNA-dependent DNA polymerase from avian sarcoma-leukosis viruses. The minimum chain length required for the priming activity to be exposed varied depending on the nucleotide sequence of the primer and thus of the primer-binding sequence of the template RNA, ie, a sudden and max increase of the priming activity was observed at a primer chain length of between 2 and 4 for poly(dG) and between 6 and 8 for poly(dT) synthesis. The observed difference in the minimum chain length seems to parallel the difference in physical stability between poly(C)-oligo(dG) and poly(A)-oligo(dT) hybrids, although the primer chain lengths are shorter than those required for the respective hybrids paired at the reaction temperature. In influenza virus RNA-dependent cDNA synthesis, the priming activity of oligonucleotides complementary to the 3' terminal sequence of vRNA segments was enhanced at a chain length of between 10 and 12, maintaining a plateau thereafter. This unexpected requirement for long primers in influenza cDNA synthesis might reflect the unique conformation of vRNA, which forms a panhandle-like structure through intramolecular pairing between 3' and 5' termini. Phosphorylation of the 5' terminus inactivated oligo(dT) to a level of a few percent of the 5'-hydroxyl oligo(dT) in priming poly(A)-dependent poly(dT) synthesis, implying that the 5' phosphate interferes with the priming activity of oligonucleotides by a yet unidentified mechanism. However, the observed interference decreased concomitantly with increase of primer chain length. (Author abstract) (33 Refs)

47. GENETIC STRUCTURE AND TRANSFORMING SEQUENCE OF AVIAN SARCOMA VIRUS UR2.

Wang LH, Hanafusa H, Notter MF, Balduzzi PC
Rockefeller Univ., New York, NY, 10021
J Virol; 41(3):833-841 1982

We have recently shown that a newly isolated avian sarcoma virus, UR2, is defective in replication and contains no sequences homologous to the src gene of Rous sarcoma virus. In this study, we analyzed the genetic structure and transforming sequence of UR2 by oligonucleotide fingerprinting. The sizes of the genomic RNAs of UR2 and its associated helper virus, UR2AV, were determined to be 24S and 35S, respectively, by sucrose gradient sedimentation. The mol wt of the 24S UR2 genomic RNA was estimated to be 1.1 x 10(6), corresponding to 3,300 nucleotides, by gel electrophoresis under the native and denatured conditions. RNase T1 oligonucleotide mapping indicated that UR2 RNA contains seven unique oligonucleotides in the middle of the genome and shares eight 5'- and six 3'-terminal oligonucleotides with UR2AV RNA. From these data, we estimated that UR2 RNA contains a unique sequence of about 1.2 kilobases in the middle of the genome, and contains 1.4 and 0.7 kilobases of sequences shared with UR2AV RNA at the 5' and 3' ends, respectively. Partial sequence analysis of the UR2-specific oligonucleotides by RNase A digestion revealed that there are no homologous counterparts to these oligonucleotides in the RNAs of other avian sarcoma and acute leukemia viruses studied to date. UR2-transformed non-virus-producing cells contain a single 24S viral RNA which is most likely the message coding for the transforming protein of UR2. On the basis of the uniqueness of the transforming sequence, we concluded that UR2 is a new member of the defective av ian sarcoma viruses. (Author abstract) (37 Refs)

48. AT LEAST TWO REGIONS OF THE VIRAL GENOME DETERMINE THE ONCOGENIC POTENTIAL OF AVIAN LEUKOSIS VIRUSES.

Robinson HL, Blais BM, Tsichlis PN, Coffin JM
Worcester Foundation Experimental Biology, Shrewsbury, MA, 01545
Proc Natl Acad Sci USA; 79(4,part1):1225-1229 1982

Recombinants of oncogenic and nononcogenic avian leukosis viruses were tested for their oncogenic potential in chickens. The results indicate that at least two regions of the viral genome determine the oncogenic potential of these viruses. The first region contains sequences that control viral mRNA synthesis. These sequences determine the potential of a virus to induce a low incidence of lymphomas, carcinomas, chondrosarcomas, fibrosarcomas, and osteopetrosis. The second region lies outside the sequences that control viral mRNA synthesis. These sequences determine the ability of a virus to induce a high incidence of lymphomas or osteopetrosis. (Author abstract) (41 Refs)

49. SIMIAN VIRUS 40 LARGE TUMOR ANTIGEN: A 'RNA BINDING PROTEIN'?

Khandjian EW, Loche M, Darlix JL, Cramer R, Turler H, Weil R
Dept. Molecular Biology, Univ. Geneva, 1211 Geneva, Switzerland
Proc Natl Acad Sci USA; 79(4,part1):1139-1143 1982

Simian virus 40 large tumor antigen was isolated by immunoaffinity chromatography from monkey or mouse cell cultures undergoing lytic or transforming infection. RNase-treated gel-purified large tumor antigen, on hydrolysis with alkali, gave about equimolar amounts of AMP, CMP, and UMP. Furthermore, RNA fragments of approx 45 nucleotides could be isolated from large tumor antigen purified by the same procedure. Mapping of the T1 oligonucleotides showed a high complexity, as indicated by the presence of unique sequences of 15-30 nucleotides and of poly(A). This is compatible with the hypothesis that these RNA fragments are derived from cellular pre-mRNAs or mRNAs. Our results suggest that Simian virus 40 large tumor antigen is a RNA-binding protein and might possibly be involved in regulation of synthesis, maturation, or translation of cellular mRNAs. (Author abstract) (39 Refs)

50. CURRENT CANCER RESEARCH ON ANTICANCER DRUGS: PRECLINICAL PHARMACOLOGY AND EFFECTIVENESS (SPECIAL LISTING).

International Cancer Research Data Bank Program Office
NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Anticancer Drugs: Preclinical Pharmacology and Effectiveness (Special Listing) This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-929302:; 93pp. 1981

Special Listings of Current Cancer Research Projects are a service of the International Cancer Research Data Bank (ICRDB) program of the National Cancer Institute. Each listing contains descriptions of ongoing projects in one selected cancer research area. The descriptions are provided by cancer scientists in about 50 different countries. Preclinical pharmacology and effectiveness of anticancer drugs is discussed with respect to absorption, transport, and distribution (liposomes, proteins, and other carriers); metabolism of anticancer drugs; toxicity (cardiotoxicity), mutagenicity and carcinogenicity; effectiveness (combination chemotherapy, combined chemo- and radiotherapy, combined chemo- and immunotherapy, drug resistance, new model systems for studying effectiveness, structure-activity studies, and other studies); effects on nucleic acids (physiochemical studies of anticancer drug-DNA complexes, induction of DNA-strand breaks and inhibition of repair, effects of anticancer drugs on processing and translation of RNA); effects of anticancer drugs on metabolism of purines and pyrimidines, folates, and other enzyme systems and metabolism; effects of anticancer drugs on cell cycle and membranes; and general pharmacological studies of anticancer drugs.

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RNA TRANSCRIPTION/ SYNTHESIS

1. CYTOCHEMICAL AND AUTORADIOGRAPHIC STUDY OF THE EARLY NUCLEAR LESIONS INDUCED BY AN ELLIPTICINE DERIVATIVE IN ISOLATED RAT HEPATOCYTES.

Sales N, Puvion E
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Eur J Cancer Clin Oncol; 18(3):291-306 1982

Isolated rat liver cells maintained in primary culture were treated with 9-OH ellipticinium (9-OH E +). The effects of this drug on the nuclear ultrastructure and on the chromatin transcriptional activity were studied by the combination of cytochemistry with high resolution autoradiography. At a low concentration (1 ug/ml) for periods ranging from 10 min to 3 hr, 9-OH E+ induced chromatin clumping, nucleolar microsegregation and a diminution in the number of perichromatin and interchromatin fibrils. Autoradiography revealed that this compound inhibited rapidly the incorporation of [5-3H]-uridine in the nucleus, preferentially but not exclusively in the nucleolar area. In addition, the distribution of the radioactivity in the nucleoli proved that the processing of the pre-ribosomal ribonucleic acids (pre-rRNA) synthesized in the presence of the drug was blocked while the processing during 9-OH E + treatment of normally synthesized pre-rRNA was not altered. These findings suggest that the inhibition of pre-rRNA processing might result from an impairment of factors controlling this processing rather than from a direct action of 9-OH E + or pre-rRNA molecules. (Author abstract) (36 Refs)

2. MOLECULAR EVENTS BASIC TO CELLULAR RADIATION RESPONSE.

Kolodny GM
Radiology Res. Lab., Massachusettes General Hosp., Boston, MA
Aerosp Med Biol; (229):14 1982

The initiation and control of the division process in normal cells to gain insight into changes caused by x-irradiation and neoplasia was discussed. It is suggested that small mol wt RNA acts as primer for new RNA synthesis by hybridizing with DNA and there initiating the transcription of a new RNA chain. It is indicated that small mol wt RNA will induce the production of new protein. It is demonstrated that RNA is taken up from the media by cells in culture and induce in vitro the production of differential cell products. (Author abstract)

3. SERUM ENHANCES THE CYCLING AND SURVIVAL OF HELA CELLS TREATED WITH 5,6-DICHLORO-1-BETA-D-RIBOFURANOSYLBENZIMIDAZOLE.

Tamm I, Kikuchi T, Murphy JS
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Proc Natl Acad Sci USA; 79(8,part1):2569-2573 1982

We have defined the growth kinetics of HeLa cell populations by determining the frequencies of mitoses and deaths and the lengths of intermitotic intervals. This was done by time-lapse cinemicrography. Untreated control cells proliferated at closely similar rates in medium enriched with 5% or 15% fetal calf serum, with an average of 4% dividing and less than 0.1% dying per hr. The mean intermitotic interval was 16 hr during exponential growth of the control populations. In contrast, in cultures treated with 40 or 60 uM 5,6-dichloro-1-beta-ribofuranosylbenzimidazole (DRB), a selective inhibitor of heterogeneous nuclear RNA synthesis, the frequency of mitoses was markedly and directly dependent on serum concentration, whereas the frequency of deaths was inversely dependent. DRB prolonged the intermitotic interval in cells cycling in the presence of the drug, but the effect was less in 15% than in 5% serum. After prolonged treatment of HeLa cells with DRB, the inhibition of heterogeneous nuclear RNA synthesis by DRB appeared to be reduced, which was not due to inactivation of DRB in the culture medium. (Author abstract) (24 Refs)

4. DIFFERENTIAL EFFECT OF DEXAMETHASONE ON FRIEND LEUKEMIA CELLS INDUCED TO DIFFERENTIATE BY HEXAMETHYLENEBISACETAMIDE OR BUTYRIC ACID.

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Cell Biol Int Rep; 6(4):341 1982

The effects of dexamethasone (DEX) on erythroid function in murine Friend leukemia (FL) cells, clone DS19-4, induced to differentiate by hexamethylenebisacetamide (HMBA) or butyric acid (BA) were investigated. Synthesis and translation of alpha- and beta-globin mRNA and Hb accumulation were greatly inhibited by DEX in the HMBA-induced cells. DEX had no effect on these functions in the BA-induced cells. The results suggest that HMBA and BA modulate gene expression in FL cells via a different mechanisms. The DS19-4 cells cultured with BA may share cellular properties in common with FL clones resistant to DEX inhibition of HMBA-induced erythroid differentiation. (5 Refs)

5. TUMOR PROMOTERS INCREASE THE SYNTHESIS OF A 32,000-DALTON PROTEIN IN BALB/C 3T3 CELLS.

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Proc Natl Acad Sci USA; 79(6,part1):1800-1804 1982

The effect of 12-O-tetradecanoylphorbol 13-acetate (TPA), a potent tumor promoter, on the synthesis of proteins in BALB/c 3T3 mouse fibroblasts has been studied. When [35S]methionine-labeled proteins synthesized after the addition of TPA were analyzed by one- or two-dimensional polyacrylamide gel electrophoresis, the increased synthesis of a 32,000-dalton protein (designated p32) was noted as one of the earliest changes. The synthesis of p32 increased approx two-fold within 2 hr at a promoter concentration of 20 ng/ml. Phorbol 12,13-didecanoate, another potent tumor promoter, showed the same effect as TPA, whereas 4-O-methyl-TPA, which has little promoting activity, did not enhance the synthesis of p32 at the same concentration but did effect a slight increase at 1 ug/ml. p32 differed immunologically from a major excreted protein discovered by Gottesman. The increased rate of the synthesis of p32 was considered to be regulated at the transcriptional level, because the increase in synthesis of p32 was inhibited by actinomycin D, and TPA-treated cells were shown to contain a higher level of translatable mRNA coding for p32 than do control cells. A possible relationship between the increase in p32 synthesis and transformation is discussed. (Author abstract) (49 Refs)

6. TEMPERATURE-SENSITIVE CHANGES IN THE STRUCTURE OF GLOBIN CHROMATIN IN LINES OF RED CELL PRECURSORS TRANSFORMED BY TS-AEV.

Weintraub H, Beug H, Groudine M, Graf T
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Cell; 28(4):931-940 1982

Chicken bone marrow cells infected in vitro with a temperature-sensitive avian erythroblastosis virus fail to produce hemoglobin at 36 C. When the product or products of the transforming gene (erb) are inactivated by a temperature shift to 42 C in culture, several different cloned lines of cells infected with the temperature-sensitive avian erythroblastosis virus begin to make hemoglobin. This shift in phenotype correlates with an increase in hemoglobin mRNA specific to both adult and embryonic alpha and beta globin. The switch is accompanied by the acquisition of DNAase I-hypersensitive sites in one cell line (clone 2); however, a hypothetically more mature line (clone 3) has already acquired globin DNAase-hypersensitive sites but does not express hemoglobin until the temperature shift. Several (but not all) specific restriction sites associated with both the alpha and beta domains become unmethylated after the switch from 36 C to 42 C. The magnitude of these methylation switches is small compared with changes that occur in these genes during normal avian erythropoiesis. The results suggest that changes in chromosomal structure precede transcription and are not a consequence of transcription. Since (presumptive) precursor cloned lines can be established with some, but not all, of the structural properties of active globin chromatin, it is likely that many of these properties can be independently established and are not obligatorily related. (Author abstract) (41 Refs)

7. TRANSCRIPTION OF ADENOVIRUS CORES IN VITRO: MAJOR RNA PRODUCTS DIFFER FROM THOSE MADE FROM A DNA TEMPLATE.

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Proc Natl Acad Sci USA; 79(6,part1):1834-1838 1982

Intact cores of adenovirus type 5 were transcribed in vitro in extracts derived from uninfected HeLa cells, and the products were analyzed by hybridization to restricted viral DNA. Predominant transcripts from cores were distinctly different from transcripts generated from deproteinized DNA. The extracts contained RNA polymerase II and RNA polymerase III. Transcription from cores was completely inhibited by low levels of alpha-amanitin, and there was little or no hybridization of products to the region of the genome encoding the small polymerase III-dependent virus-associated RNA that was major transcript from the DNA template. The major transcripts from cores hybridized to the rightward-transcribed strand of the region between 75 and 89 map units, early region 3 of the adenovirus genome. There was several-fold more transcription of this region in cores than of the region downstream from the major late promoter, which predominates among polymerase II transcripts from DNA. (Author abstract) (38 Refs)

8. TRANSCRIPTION OF THE HEPATITIS B SURFACE ANTIGEN GENE IN MOUSE CELLS TRANSFORMED WITH CLONED VIRAL DNA.

Pourcel C, Louise A, Gervais M, Chenciner N, Dubois MF, Tiollais P
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J Virol; 42(1):100-105 1982

Mouse L cells transformed with recombinant plasmids carrying hepatitis B virus (HBV) DNA fragments were used to study the transcription of the viral surface antigen gene (gene S). An HBV-specific, polyadenylated, 2.3-kilobase RNA was mapped on the HBV genome. This RNA hybridized with approx 75% of the genome and excluded the region of the HBV core antigen gene (gene C). The 2.3-kilobase RNA species was present only in cell lines that produced hepatitis B surface antigen. An HBV-specific 2.3-kilobase RNA was also detected in human hepatoma cell line PLC/PRF/5 which produced hepatitis B surface antigen. A study of gene S expression in the transformed mouse L cells allowed us to localize the regions of initiation and termination of gene S transcription. Our results strongly suggest that the 2.3-kilobase RNA molecule is the mRNA of the major polypeptide of the envelope, which carries the viral surface antigen determinants. (Author abstract) (21 Refs)

9. INTRACISTERNAL A-PARTICLE GENES: STRUCTURE OF ADJACENT GENES AND MAPPING OF THE BOUNDARIES OF THE TRANSCRIPTIONAL UNIT.

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J Virol; 42(1):123-130 1982

Adjacent intracisternal A-particle (IAP) genes were identified in two different recombinant DNA clones, lambda81 and lambda19. In clone lambda81, the most common form of IAP gene was separated by 5.3 kilobases from another IAP gene that had two apparent internal deletions. The two genes were in a head-to-tail configuration. In clone lambda19, two different types of IAP genes were separated by less than 0.5 kilobase. Blot hybridization analysis of mouse DNA demonstrated that the DNA sequence found in clone lambda81 is identical to the in vivo configuration. Using isolated DNA fragments from clone lambda19, we mapped the boundaries of the IAP RNA by S1 digestion of RNA-DNA hybrids and by cDNA extension. With these techniques, both the 5' end and the 3' end of the IAP RNA in two different plasmacytomas (MOPC 315 and TEPC 15) were shown to fall within the long terminal direct repeat of the IAP gene. The fragment sizes generated by S1 digestion of IAP RNAs isolated from the two tumor lines were found to differ, indicating that different IAP genes may be transcribed in these two plasmacytomas. (Author abstract) (31 Refs)

10. SPECIFIC SMALL NUCLEAR RNAS FROM SV40-TRANSFORMED CELLS STIMULATE TRANSCRIPTION INITIATION IN NONTRANSFORMED ISOLATED NUCLEI.

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Can J Biochem; 60(3):252-262 1982

Previous studies in our laboratory have implicated small nuclear RNAs (SnRNA) in the regulation of transcription in isolated mammalian cell nuclei. The present investigation was designed to develop a transcription assay system using isolated intact nuclei with optimized RNA polymerase II activity which would be capable of reinitiation in vitro to study the mode of action of the 'active' RNA. We used nuclei isolated from either human WI38 or Balb 3T3 mouse cells to test the activity of SnRNA purified from SV40-transformed WI38 or 3T3 cell lines. These systems were found to support transcription up to 60 min, 40-60% of which was polymerase II dependent. In vitro initiations were detected by [gamma-32P]ATP incorporation as well as by Hg-Sepharose chromatography using (gamma-S)ATP as substrate. Results supported the following conclusions: (a) SnRNA from transformed cells stimulates the transcriptional activity of nontransformed nuclei while homologous SnRNA has little or no activity; (b) the stimulation is NaOH-sensitive and is dependent on RNA polymerase II since it is eliminated by 1 ug/mL alpha-amanitin; (c) the active subfraction of SnRNA from mouse cells was found to be of identical size (320-350 nucleotides) to that previously identified in human and monkey cells; and (d) analysis of the transcripts obtained from control and stimulated cell nuclei revealed that

SnRNA activity is due primarily to an increase in the number of initiated chains. (Author abstract) (35 Refs)

11. RNA SYNTHESIS IN THE PRESENCE OF TRANSFER RNA BY DNA-DEPENDENT RNA POLYMERASE II FROM MOUSE ASCITES SARCOMA CELLS.

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Arch Biochem Biophys; 215(1):179-182 1982

Characteristics of RNA synthesis by DNA-dependent RNA polymerase II (RPII) from mouse ascites sarcoma cells are reported. Incorporation of uridine monophosphate into an acid-insoluble fraction was catalyzed by RPII in the presence of transfer RNA (tRNA). RNA synthesis was inhibited by alpha-amanitin but not by DNase or actinomycin D. RNA synthesis was dependent on the presence of nucleoside triphosphate and manganese ions. The RNA synthesized was digestible by RNase A. Results indicate that RNA synthesis by mouse sarcoma RPII is dependent on tRNA. (11 Refs)

12. ACTIVATION OF NON-EXPRESSED BOVINE PAPILLOMA VIRUS GENOMES BY TUMOUR PROMOTERS.

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Nature; 296(5858):675-677 1982

Following infection of mouse embryo fibroblasts (MEF), bovine papilloma virus type 1 (BPV-1) genome resides in a non-expressed episomal state. After passaging of the BPV-1 infected cells, the viral DNA is eventually lost due to failure to replicate, as shown by hybridization of the viral DNA to a BPV-1 DNA probe according to the Southern method. When BPV-1-infected MEF cells were treated with the tumor promotor 12-O-tetradecanoylphorbol-13-acetate (TPA), considerably more BPV-1 DNA was found after 4 days than in the non-treated cells. Even when TPA was administered to cells in the passage 3 after infection, viral DNA could be detected while none was detectable in non-treated passage 3 cells. Viral DNA was detected at passages 1 and 5 after TPA removal, indicating that BPV-1 DNA continues to replicate in the absence of TPA. TPA also promoted viral transcription. While no viral RNA sequences could be detected in untreated MEF cells one passage after infection, 4 days after TPA treatment of a parallel culture, several species of BPV-1 RNA were found. The same RNA species were detected in BPV-1-induced hamster embryo fibroblasts. Similar results to TPA were obtained with 12-O-retinoylphorbol-13-acetate (RPA). In addition to induction of viral transcripts, TPA induced a transformed phenotype, expressed by an increase in saturation density of the cultures and the ability to grow in low serum medium. While several primate cell lines showed none of these effects, bovine fetal thyroid (BFT) cells did exhibit an enhanced DNA replication and a transient transcription and phenotypic transformation in the presence of TPA and RPA. Tumor promoter-treated MEF and BFT cells may provide a system for studying the amplification and expression of foreign genes inserted into a BPV-1 vector as well as a screening system for putative tumor-promoting agents. (22 Refs)

STUDIES OF HETEROGENEOUS NUCLEAR RNA

13. PRESENCE OF THE PRE-MRNA FOR THE 72K DNA BINDING PROTEIN IN HNRNP FROM EARLY ADENOVIRUS-2 INFECTED HELA CELLS.

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Biochem Biophys Res Commun; 105(2):603-609 1982

An investigation was made on the RNa transcribed from adenovirus-2 (Ad-2) early region E2, which codes for the 72,000 dalton DNA binding protein (72K DBP). Tritium-labeled ribonucleoprotein particles (RNP) prepared from Ad-2 infected HeLa cells were deproteinized and the labeled RNA was hybridized to the EcoRI B DNA restriction fragment bound to a nitrocellulose filter. This DNA fragment carries the 3' half of the 72K DBP gene. EcoRI B specific RNA from nuclear RNP (hnRNP) was found in structures sedimenting in a sucrose gradient between 70 and 200S, while EcoRI B specific RNA from cytoplasmic RNA was found in a narrow distribution around 50S. Polyacrylamide gel electrophoresis of the RNA from the early Ad-2 transcripts showed a single 18S species in the cytoplasmic RNP in contrast to nuclear RNP, which showed a heterodisperse distribution of RNa in the 28S to 10S range. Previous studies indicate three size classes of nuclear RNA transcribed from the early region E2: a 28S pre-mRNA which is the first polyadenylated species likely to occur by cleavage of the primary transcript and which contains two intervening sequences, a 23S intermediate RNA and a 20S mature mRNA. These data indicate that, except for the species smaller than 18S which are degradation products, the newly synthesized intact transcripts of the gene coding for Ad-2 72K DBP are present in large hnRNP. Northern blot hybridization of RNA from early Ad-2 transcripts to EcoRI B DNA revealed that the EcoRI B probe hybridized to two components which correspond to the unspliced 28S pre-mRNA and to the mature 18S mRNA; the 23S transitory species was not observed. This demonstrates, in addition to the unspliced 28S pre-mRNA, the existence of mature mRNA molecules in nuclear RNP which differ in sedimentation coefficient from cytoplasmic mRNP. (30 Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

14. SEQUENCE HOMOLOGY BETWEEN POLYADENYLATED MRNAS FROM TRANSPLANTABLE MOUSE TUMOURS OF DIFFERENT ORIGIN, AS COMPARED TO MRNAS FROM NORMAL ADULT OR EMBRYONIC TISSUES.

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Eur J Biochem; 123(2):407-414 1982

Complementary DNA copies (cDNA) were 3H-labeled and cell-free-synthesized on polyadenylated mRNA templates which had been isolated from the cytoplasm of mouse FLS ascites tumor cells. They were hybridized to RNAs from different mouse origins: ascites tumors (FLS, Ehrlich, Krebs 2) passaged in mice, tissue-cultured Friend erythroleukemia cells, adult liver, adult brain and whole embryos, 10-12 days old. Analysis of the cDNA-RNA reassociation kinetics showed that the total molecular complexity of FLS cells poly(A)-rich RNA is equivalent to 11,000-12,000 different sequences of 1,800 residues each, distributed in the three usual classes of high, middle and low abundancies. All or nearly all of these sequences were also found in Ehrlich and Krebs 2 tumor cells with the same frequency distribution as in FLS cells. When comparing the total number and relative abundancies of poly(A)-rich RNA sequences in ascites tumor cells to other mouse cells, we found slight but reproducible differences for Friend erythroleukemia, more pronounced differences for adult liver or whole embryos, and maximal differences for adult brain. Some of the most abundant poly(A)-rich RNA species common to all tumor strains either did not exist or were much less abundant in normal tissues. Furthermore, the abundant poly(A)-rich RNA sequences which are common to ascites tumor cells and fetal tissues were also found with the same frequency distribution in adult liver, where cell proliferation is negligible. This supports the conclusion that most of the frequent poly(A)-rich sequences, which appeared to be tumor-specific, cannot simply represent normal mitosis gene transcripts and might in fact be related to the expression of malignancy, at least in old-established tumor strains of different tissue origins. (Author abstract) (56 Refs)

15. REGULATION OF 2-5 A SYNTHETASE ACTIVITY AND ANTIVIRAL STATE IN INTERFERON TREATED CHICK CELLS.

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Biochem Biophys Res Commun; 105(2):412-418 1982

The activity of 2'-5'oligoadenylate synthetase (2-5 A synthetase) and the antiviral state (AVS) of chick embryo fibroblasts following interferon (IFN) treatment were investigated. 2-5 A synthetase increased during IFN treatment and rose to a maximun level in 5-6 hr, remaining at this level as long as IFN was present in the culture medium. The AVS, measured by the inhibition of Sindbis virus yield, exhibited similar kinetics. Following removal of IFN, both the 2-5 A synthetase activity and the AVS were maintained for 9-10 hr, after which the activity decayed. If cycloheximide was added to the culture immediately following removal of IFN, this decay was not observed; both activities remained at the 5-6 hr peak level. This effect suggests that the decrease of 2-5 A synthetase is controlled by an unstable regulatory protein. To test if this regulation is due to either degradation of 2-5 A synthetase or reversible activation, the cells were treated for 6 hr with IFN, the IFN removed for the next 24 hr, and cycloheximide then added at 30 hr. For both the 2-5 A synthetase and AVS, removal of IFN again lead to a decay; however, inhibition of protein synthesis by cycloheximide at 30 hr produced an increase in both activities to the same level as when IFN was removed at 6 hr. This further suggests that an unstable protein reversibly inactivates the enzyme activity. In the same experiments, removal of cycloheximide after 18 hr produced a 'superinduction', an increase in the 2-5 A synthetase activity and AVS. This may be explained by the accumulation of mRNA for 2-5 A synthetase during the period of cycloheximide treatment, this mRNA being transiently inactivated by factors which require protein synthesis. (17 Refs)

16. DIFFERING RESPONSES OF GLOBIN AND GLYCOPHORIN GENE EXPRESSION TO HEMIN IN THE HUMAN LEUKEMIA CELL LINE K562.

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Blood; 59(4):738-746 1982

The human leukemia cell line, K562, produces embryonic and fetal hemoglobins and glycophorin A, proteins normally associated only with erythroid cells. Hemoglobin accumulation is enhanced by exposure of the cells to 0.05 mM hemin. We have examined K562 cells before and after exposure to hemin to determine whether expression of these erythroid proteins was shared by all cells or confined to specific subpopulations. Globin gene expression was examined by quantitation of globin mRNA sequences, using a 3H-globin cDNA molecular hybridization probe. Constitutive cells produced globin mRNA, the content of which was increased three-four-fold by hemin. Cell-to-cell distribution of globin mRNA was determined by in situ hybridization of 3H-globin cDNA to constitutive and hemin-treated K562 cells. Virtually all cells in the culture exhibited grain counts above background, indicating globin gene expression by all cells, rather than a confined subpopulation. Virtually all hemin-treated cells had three-five-fold higher grain counts, indicating uniformly increased globin gene expression. The glycophorin content of K562 cells was estimated by fluorescence-activated cell sorting (FACS) of cells labeled with fluorescein-labeled antiglycophorin antiserum. The vast majority of constitutive cells contained glycophorin, but exhibited no apparent increase in glycophorin accumulation after hemin exposure. Thus, glycophorin and globin genes exhibited differential responses to hemin. These differences could reflect normal differences in the patterns of specialized gene expression in stem cells. Alternatively, different aberrations of gene expression could be occurring in response to the determinants of the neoplastic properties of K562. (Author abstract) (32 Refs)

17. IDENTIFICATION AND PURIFICATION OF A PROTEIN ENCODED BY THE HUMAN ADENOVIRUS TYPE 2 TRANSFORMING REGION.

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J Virol; 42(1):30-41 1982

The human adenovirus Type 2 (Ad2) transforming genes are located in early regions E1a (map position 1.3 to 4.5) and E1b (map position 4.6 to 11.2). We have identified and purified to near homogeneity a major 20,000-mol-wt (20K) protein and have shown that it is coded by E1b. Using an Ad2-transformed cell antiserum which contained antibody to E1b-coded proteins, we immunoprecipitated 53K and 19K proteins from the nucleoplasm and 53K, 19K, and 20K proteins from the cytoplasmic S-100 fraction of Ad2 productively infected and Ad2-transformed cells. The 19K protein was present in both the nucleoplasm and the cytoplasm, where the 20K protein was found only in the cytoplasm. The 53K and 19K proteins are known Ad2 E1b-coded proteins. The 20K protein was purified to near homogeneity in 20 to 50% yields by sequential DEAE-Sephacel chromatography and reverse-phase high-performance liquid chromatography. Purified 20K protein shares most of its methionine-labeled tryptic peptides with E1b-53K, as shown by reverse-phase high-performance liquid chromatography, and therefore is closely related to the 53K protein. The 19K protein does not appear to share tryptic peptides with either 20K or 53K protein. To provide more direct evidence that 20K protein is virus-coded we translated E1b-specific mRNA in vitro. Both immunoprecipitation analysis and high-performance liquid chromatography purification of the translated product identified a 20K protein that has the same tryptic peptides as the 20K protein isolated from infected and from transformed cells. These findings suggest that the Ad2 20K protein is a primary translation product of an Ad2 E1b mRNA. (Author abstract) (39 Refs)

18. SUBGENOMIC MRNA IN OK10 DEFECTIVE LEUKEMIA VIRUS-TRANSFORMED CELLS.

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J Virol; 42(1):71-82 1982

OK10, a defective leukemia virus, is produced as a defective particle by so-called nonproducer transformed quail fibroblasts. OK10 defective viral particles contain an 8-kilobase (kb)-long genomic RNA, lack any detectable reverse transcriptase activity, and are not infectious. We studied the genetic content of OK10 RNA extracted from both virions and infected cells. About 77% of the OK10 8.0-kb RNA was related to avian leukosis viruses in the three structural genes gag, pol, and env, as well as in the c region. The remainder of the OK10 genome-encoding capacity was homologous to the MC29-specific transforming sequence myc(m) and has been named myc(o). Heteroduplex molecules formed between the viral OK10 8.0-kb RNA and the 6.8-kb SacI DNA fragment of the Prague A strain of Rous sarcoma virus indicated that the myc(o) sequence formed a continuous RNA stretch of 1.4 to 1.6 kb long between Delta-pol and Deltaenv. We also examined the myc(o)-containing mRNA's transcribed in OK10-transformed cells. In OK10-transformed bone marrow cells (OK10 BM), a stable bone marrow-derived cell line producing OK10, the myc(o) sequence was found in four RNA species of 11.0, 8.0, 7.0, and 3.6 kb. Again, the genetic content of these mRNA's indicated that (i) the 3.6-kb species could be spliced out of the 8.0-kb-genome size mRNA and (ii) the 11.0-kb-long mRNA could represent a read-through of the OK10 provirus, the corresponding maturation product being, then, a 7.0-kb mRNA. In conclusion, whereas the myc sequences have been generally thought to be expressed through a gag-onc fusion protein, as for MC29 and CMII viruses, our experiments indicate that they could also be expressed as a non-gag-related product made from a subgenomic mRNA in the OK10 transformed cells. (34 Refs)

19. CLONED CDNA SEQUENCES OF THE HYPOXANTHINE/GUANINE PHOSPHORIBOSYLTRANSFERASE GENE FROM A MOUSE NEUROBLASTOMA CELL LINE FOUND TO HAVE AMPLIFIED GENOMIC SEQUENCES.

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Howard Hughes Medical Inst. Lab., Baylor Coll. Medicine, Houston, TX, 77030
Proc Natl Acad Sci USA; 79(6,part1):1950-1954 1982

Cloned cDNA sequences of the murine hypoxanthine/guanine phosphoribosyltransferase (HPRT; EC 2.4.2.8) gene have been isolated by using a mouse neuroblastoma cell line containing increased levels of a variant HPRT protein. We have used these sequences as probes to demonstrate that protein over-production in this cell line is a consequence of a least a 20-fold increase in HPRT mRNA levels resulting from approximately 50-fold amplification of HPRT genomic sequences. The largest cDNA insert so far characterized represents about 70% of the HPRT mRNA sequence. This cDNA is shown to possess regions of homology with mRNA and DNA from Chinese hamster, baboon, and human, thus facilitating detailed analysis of this locus in these four species. (Author abstract) (33 Refs)

20. MOUSE SPLEEN AND IGD-SECRETING PLASMACYTOMAS CONTAIN MULTIPLE IGD DELTA CHAIN RNAS.

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Nature; 296(5856):459-462 1982

Fragments of 32P-labelled DNA prepared from a delta cDNA clone and a delta genomic clone, obtained from normal mouse spleens and two gamma messenger RNA (mRNA)-containing, IgD-secreting mouse plasmacytomas TEPC 1017 and TEPC 1033, were used to characterize by hybridization the delta RNAs fractionated on methyl mercury hydroxide agarose gels. Normal mouse spleens contained a major 2.9 kilobase (kb) and a minor 2.1 kb RNA encoding membrane-bound delta chain (gamma-m) RNA plus a 1.75-kb RNA encoding secreting delta chains. Less abundant delta RNA species (2.65 and 3.2 kb) were also observed. Different gene segments or combinations of segments were used in the 3' termini of the multiple delta RNAs. The results indicated that the delta chain is unusual among immunoglobulins in that its mRNA may exist in many forms. Delta RNA in spleen and in TEPC 1017 and TEPC 1033 which encode the membrane forms of delta chain and share certain significant characteristics were identified. Most important, a hydrophobic polypeptide is encoded in both the 2.9-and and the 2.1 kb delta-m mRNA found in the spleen and the plasmacytomas. Implications of the findings are discussed. (35 Refs)

21. MOLECULAR BIOLOGY CRITERIA FOR THE FUNCTION OF ROUS SARCOMA VIRUS GENE IN TRANSFORMED KHS RAT CELLS.

Kiselev FL, Galetskii SA, Mazurenko NN, Asanova AA, Zborovskaia IB, Topol' LZ
All-Union Oncology Res. Center, USSR Acad. Medical Sciences, Moscow, USSR
Mol Biol (Mosk); 16(1):66-76 1982

Integration, transcription and translation of Rous sarcoma virus (RSV) genome was studied in (non-virus-producing) transformed rat fibrosarcoma XC cells. About 10 copies of RSV genome were integrated into the host cell genome. Different types of viral RNAs, identified in the cytoplasmic fraction, had sedimentation values similar to those for RSV-specific RNAs in virus-producing chicken cells. These RNAs were translated in polysomes and directed the synthesis of gag, env and src proteins. Compared with chicken cells, the cleavage of gag precursor Pr 76gag was not observed in transformed XC cells. (30 Refs) (In RUS)

22. DETAILED STRUCTURAL ANALYSIS OF TWO SPLICED HSV-1 IMMEDIATE-EARLY MRNAS.

Rixon FJ, Clements JB
Inst. Virology, Univ. Glasgow, Glasgow G11 5JR, Scotland
Nucleic Acids Res; 10(7):2241-2256 1982

The structures of two HSV-1 immediate-early mRNAs have been determined by nuclease-digestion procedures using 5' and

3' end-labeled DNA probes. These mRNAs, which map across the junctions between the short unique (US) and short repeat (IRS and TRS) genome regions, have common 5' portions located in IRS and TRS. The 3' portions, which extend into opposite ends of US, are unique. The DNA sequence encoding the common 5' portions largely comprises a 247 base pair (bp) leader region and a single intron of variable size. The variation in intron length is due to different copy numbers of a 22 bp tandem reiteration. A small proportion of the mRNA population is unspliced, but otherwise is identical to the more abundant spliced species. (Author abstract) (38 Refs)

23. VIRUS-SPECIFIC TRANSCRIPTION IN BOVINE PAPILLOMAVIRUS-TRANSFORMED MOUSE CELLS.

Heilman CA, Engel L, Lowy DR, Howley PM
Lab. Carcinogen Metabolism, NCI, Bethesda, MD, 20205
Virology; 119(1):22-34 1982

We have characterized the viral-specific RNAs present in C127 mouse cells transformed by the BPV-1 virus or by cloned DNA. Five distinct BPV-1 polyadenylated RNA species can be detected by size fractionation on denaturing formaldehyde agarose gels, measuring 1050, 1150, 1700, 3800, and bases. These RNA species are all transcribed from the same DNA strand and, map to a region between 0.34 and 0.85 map units of the 8-kb BPV-1 DNA. All five viral RNA species share a common 3' terminus at 0.34 map units and the 5' ends map at approx 0.47, 0.485, 0.55, 0.785, and 0.85 map units. Analysis of the three most abundant viral RNA species (1050, 1150, and 1700 bases) did not reveal any internal splicing; but the presence of a remote 5' leader sequence could not be ruled out. (Author abstract) (37 Refs)

24. TRANSFORMATION-DEFICIENT ADENOVIRUS MUTANT DEFECTIVE IN EXPRESSION OF REGION 1A BUT NOT REGION 1B.

Solnick D, Anderson MA
Institut fuer Zell- and Tumorbiologie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
J Virol; 42(1):106-113 1982

An adenovirus Type 5 host range mutant (hr440) has been isolated which is defective in a splicing event required to generate the middle-sized mRNA from early region 1A. This defect has been ascribed to two adjacent nucleotide changes which lie five and six nucleotides from the 5' splice site for this mRNA. One of these changes introduces an amber codon into the reading frame of the largest region 1A mRNA, resulting in the production of a truncated polypeptide. Like other region 1A mutants, hr440 is defective in the production of mRNA from early regions 2 and 3, but hr440 is unusual in that transcription from regions 1B and 4 is normal. Furthermore, although region 1B expression is unaffected, hr440 does not transform baby rat kidney cells. Therefore, expression of early region 1B is insufficient for transformation, eliminating the possibility that region 1A is required only to induce such expression. (Author abstract) (41 Refs)

25. SIMIAN VIRUS 40-RABBIT BETA-GLOBIN RECOMBINANTS LACKING LATE MRNA SPLICE SITES EXPRESS CYTOPLASMIC RNAS WITH ALTERED STRUCTURES.

White RT, Berg P, Villarreal LP
Dept. Biochemistry, Univ. California, Berkeley, CA, 94720
J Virol; 42(1):262-274 1982

Deletions were introduced at exon-intron boundaries in the late region of a simian virus 40-beta-globin cDNA recombinant to study the role of splicing in the formation of simian virus 40 late cytoplasmic RNAs. The recombinant was used as a wild type because it allowed characterization of mutant RNAs expressed from defective genomes in the presence of comparable RNAs contributed by the coinfecting helper virus. Removal of a 17-base pair segment at map position 0.76, which included a portion of the leader sequence implicated in the splicing of the major 16S mRNA, prevented expression of 16S-type mRNA. The same mutant accumulated cytoplasmic 19S-type mRNA, but the assortment of the 5' ends of these mRNAs differed from the assortment in the wild-type counterparts. Another mutant that lacks nucleotide sequences implicated in the splicing of the major 16S mRNA and one of the principal 19S-type RNAs accumulated a 16S-type mRNA with a previously undetected leader splice, an assortment of 19S mRNAs with new or normally underrepresented splices, and even a species of unspliced cytoplasmic 19S mRNA. (Author abstract) (36 Refs)

26. DIFFERENTIAL EXPRESSION OF THE AMV GENE IN HUMAN HEMATOPOIETIC CELLS.

Westin EH, Gallo RC, Arya SK, Eva A, Souza LM, Baluda MA, Aaronson SA, Wong-Staal F
Lab. Tumor Cell Biology, Div. Cancer Treatment, NCI, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(7):2194-2198 1982

Total cellular RNAs from a variety of fresh and culture-derived human hematopoietic neoplastic cell types at various stages of differentiation and human sarcoma, carcinoma, melanoma, and glioblastoma cell lines were enriched for poly(A)-containing sequences, fractionated by gel electrophoresis, and blot hybridized to a cloned DNA probe containing the transforming sequences (v-amv) of avian myeloblastosis virus (AMV), a virus known to cause myeloid leukemias in chickens. Expression of RNA sequences homologous to AMV was detected in all immature myeloid and lymphoid T cells in addition to single erythroid cell line examined, but not in mature T cells or in B cells, including lymphoblast cell lines derived from patients with Burkitt lymphoma. In addition, induction of the cell line HL60, a promyelocytic leukemia line, to differentiate with dimethyl sulfoxide or retinoic acid resulted in a reduction of the level of expression of the human cellular gene c-amv homologous to v-amv. There was no detectable c-amv mRNA in any of the solid tumor cell lines examined. Thus, expression of the human c-amv gene could be correlated with the stage of differentiation of different hematopoietic cell types determines by morphologic and marker studies. Expression of c-amv could not be correlated with the extent of methylation in HL60 and in HL60 induced to differentiate with dimethyl sulfoxide. (Author abstract) (48 Refs)

27. REGULATION OF THE CELLULAR P53 TUMOR ANTIGEN IN TERATOCARCINOMA CELLS AND THEIR DIFFERENTIATED PROGENY.

Oren M, Reich NC, Levine AJ
Dept. Microbiology, Sch. Medicine, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Mol Cell Biol; 2(4):443-449 1982

The regulation of a 53,000-mol wt cellular tumor antigen, p53, in F9 embryonal carcinoma cells was investigated. Treatment of F9 cells with retinoic acid and dibutyryl ADP causes the cells to differentiate, predominantly into endoderm-like cells, and results in a marked decrease in the levels of p53. The mechanism(s) responsible for the decline in p53 in differentiated cells involves a marked decrease in the amount of in vitro translatable p53 messenger RNA. This mechanism is discussed with respect to that operating in simian virus 40 infection or transformation and which involves increased stability of the p53 protein. (22 Refs)

28. NO EVIDENCE FOR POST-TRANSCRIPTIONAL CONTROL OF ALBUMIN AND ALPHA-FETOPROTEIN GENE EXPRESSION IN DEVELOPING RAT LIVER AND NEOPLASIA.

Nahon JL, Gal A, Frain M, Sell S, Sala-Trepat JM
Laboratoire d'Enzymologie, CNRS, 91190 Gif-sur-Yvette, France
Nucleic Acids Res; 10(6):1895-1911 1982

Rot analysis of hybridization data using highly labeled alpha-fetoprotein (AFP) and albumin (32P)cDNA probes has been used to quantitate AFP and albumin mRNA sequences in RNA preparations from different subcellular fractions of developing rat liver and Morris hepatoma 7777. In addition, size analysis of these mRNA sequences has been carried out by electrophoretic fractionation on agarose gels containing methylmercury hydroxide and hybridization to radioactive cloned albumin and AFP cDNA probes. In all the tissues examined (fetal, newborn and adult rat liver, and hepatoma 7777) most of the albumin and AFP mRNA sequences were found associated with the polysomes as mature mRNA molecules; less than 2% of these sequences were present in the nuclear or the nonpolysomal cytoplasmic compartments. The number of AFP mRNA molecules was found to decrease in parallel in all the cellular compartments during rat liver development. In Morris hepatoma 7777 the content of albumin mRNA was considerably decreased in all the cellular fractions as compared to normal liver. These results demonstrate that post-transcriptional control mechanisms leading to an accumulation of non-functional mRNA molecules are not implicated in the changes of expression of albumin and AFP genes during rat liver development and neoplasia. (Author abstract) (47 Refs)

29. THE IDENTITY OF INTERFERON-BETA1 MRNA TRANSCRIPTS IN HUMAN FIBROBLASTS AND NAMALVA CELLS.

Gross G, Bruns W, Mayr W, Collins J
Abt. Genetik, Gesellschaft fur Biotechnologische Forschung mbH, Mascheroder Weg, 3300 Braunschweig, W. Germany
FEBS Lett; 139(2):201-204 1982

The messenger RNA (mRNA) for interferon-beta1 (IFN-b1) induced in different cell types by different modes of induction were compared. Synthesis of mRNA for IFN-b1 production was induced in human fibroblast cultures by exposure to cyclohexamide (50 ug/ml) and polyriboinosinic-polyribocytidylic acid (50 ug/ml). Synthesis of mRNA for IFN-b1 was induced in lymphoblastoid Namalva cells by exposure to Sendai virus for 5 hr. The DNA fragment EcoRI-F, which contains the entire IFN-b1 gene was used for S1 mapping. Klenow polymerase was used for 3'-end labeling. T4 DNA kinase was used for 5'-end labeling. Denaturing on 2% agarose gel indicated that IFN-b1 produced by the human fibroblasts was the same size as IFN-b1 produced by Namalva cells. Mapping studies indicated that mRNA for IFN-b1 induced by either system was 840 nucleotides in length without the poly(A) tail. The 5'-end labeled BglII fragment gave rise to a 640 nucleotide fragment; the 3'-end labeled fragment BglII fragment gave rise to a 200 base-pair fragment that was protected against S1-digestion. Results indicate that mRNA for IFN-b1 induced in different cell types by different induction systems can be of identical size. (15 Refs)

30. ANALYSIS OF POLYADENYLATE-PROTEIN COMPLEX OF POLYSOMAL MESSENGER RNA FROM MOUSE L CELLS.

Bernd A, Zahn RK, Maidhof A, Muller EG
(c/o Muller), Institut fur Physiologische Chemie der Universitat, Duesbergweg, D-6500 Mainz, W. Germany
Hoppe Seylers Z Physiol Chem; 363(3):221-228 1982

The organization of polysomal poly(A)-ribonucleoprotein complex [poly(A)-RNP] was studied. The poly(A)-associated proteins were liberated directly from the poly(A)-RNP complex. Polysomal mRNA was isolated from L5178y mouse lymphoma cells by oligo(dT)-cellulose chromatography; poly(A)-RNP was prepared by nuclease digestion. The poly(A)-RNP fraction was considered to be pure basing on the size of its poly(A)component which was determined to consist of 155 AMP moieties. By radiolabeling with [3H]dansyl chloride, two poly(A)-associated proteins with molecular masses of 77,000 Da (P77) and 54,000 Da(P54) were identified. In a quantitative approach, it was shown that the polysomal poly(A)-RNP complex is composed of approximately four molecules P54 and two molecules P77. Digestion experiments with dimers and tetramers containing ribonuclease A indicated that P54 covers 15-20 AMP residues and P77 a sequence of 40-45 nucleotides on the poly(A)155 stretch of polysomal poly(A)-RNP. (Author abstract) (41 Refs)

STRUCTURE AND LEVELS OF TRANSFER RNA

31. CELL GROWTH AND TRNALYS4 SYNTHESIS IN MOUSE 3T3 CELLS.

Ortwerth BJ, Wolters J, Nahlik J, Conkin-Hollingshead C
Dept. Ophthalmology, Univ. Missouri, Columbia, MO, 65201
Exp Cell Res; 138(2):241-250 1982

The RPC-5 chromatographic profiles of lys-tRNA were analyzed during the growth of 3T3 cells in culture. An inverse relationship was seen between tRNAlys2 and tRNAlys4 which was markedly influenced by medium changes. This interchange of tRNAlys2 and tRNAlys4 could be controlled by altering the levels of serum in the medium, or more precisely by altering the serum to cell ratio. A different change in lys-tRNA distribution was seen when the cells reached confluency. The amounts of tRNAlys2, tRNAlys3 and tRNAlys4 all decreased with a corresponding increase in either tRNAlys5 or tRNAlys6. An identical change in lys-tRNA could be produced by shifting sparse cells into a medium containing 10% calf plasma instead of 10% serum. Both tRNAlys profiles and cell growth were returned to normal when the cells were returned to medium with 10% fetal calf serum (FCS) or 10% calf plasma and fibroblast growth factor (FGF). A third alteration in tRNAlys profiles was seen by the addition of cAMP to the cultures. A decrease in tRNAlys5 and a corresponding increase in tRNAlys6 was seen upon the addition of 10(-3) M db-cAMP and was accentuated by the simultaneous addition of 10(-3) M methyl isobutylxanthine. These data are consistent with an ordered sequence of tRNAlys modification involving tRNAlys2, tRNAlys3, tRNAlys4, tRNAlys5B and tRNAlys6. Several of the factors which control proliferation appear to control the activity of different tRNA-modifying enzymes in this tRNAlys pathway thereby controlling the levels of tRNAlys4, a tRNA previously shown to correlate directly with the proliferative rate of cells. (Author abstract) (23 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

32. INFLUENCE OF 3-METHYLCHOLANTHRENE ON LIVER NUCLEOLAR AND NUCLEOPLASMIC ACTIVITIES OF PROTEIN KINASES AND RNA POLYMERASES.

Kleeberg U, Szeberenyi J, Juhasz P, Tigyi A, Klinger W
Inst. Pharmacology and Toxicology, Friedrich-Schiller Univ., Jena, E. Germany
Biochem Pharmacol; 31(6):1063-1067 1982

The experiments were designed to investigate some details of the action of 3-methylcholanthrene (3-MC) on the regulation of transcription. After a single intraperitoneal dose of 3-MC a significant increase in the activities of both nucleolar and nucleoplasmic protein kinases in hepatic cells of young rats was found. The maximal stimulation took place 24 hr after the administration of 3-MC and the extent of activation was much greater in the nucleolar fraction. There is a significant elevation of the activities of both functional forms, free and template-engaged, of RNA polymerase A 24 hr after a single injection of 3-MC. Free and engaged forms of extranucleolar RNA polymerase B show a different behavior: after 24 hr of 3-MC administration the engaged form is markedly enhanced while the activity of the free enzyme shows a significant decrease. The more moderate increase in total RNA polymerase B activity is obviously preceded by a transfer of the enzyme from 'free' to 'engaged' form. Since the enhancement of protein kinase activities was accompanied by the stimulation of nuclear RNA polymerases we suggest that both kinds of enzymes are involved in an epigenetic mechanism of the inducing action of 3-MC on cytochrome P1-450. (Author abstract) (47 Refs)

33. ALTERATIONS IN DNA-DEPENDENT RNA POLYMERASE I FROM RAT LIVER ACCOMPANYING ETHIONINE ADMINISTRATION.

Yamano H, Sawai Y, Thung WL, Sato F, Tsukada K
Dept. Pathological Biochemistry, Medical Res. Inst., Tokyo Medical and Dental Univ., Kandasurugadai, Chiyoda-ku, Tokyo 101, Japan
Biochem Biophys Res Commun; 105(3):799-805 1982

Repeated administration of ethionine, an hepatocarcinogen and the ethyl analogue of the amino acid methionine, was found to increase the activity of RNA polymerase I from rat liver nuclei 3-to 4-fold when given simultaneously with adenine. It is suggested that changes in RNA polymerase I levels observed after ethionine administration may constitute an important early biochemical event in the liver that triggers cellular proliferation leading to the development of neoplasia. (27 Refs)

OTHER RELATED STUDIES

34. IN VIVO BINDING OF N-NITROSOPYRROLIDINE AND N-NITROSOHEXAMETHYLENEIMINE TO NON-PURINE SITES ON RAT LIVER DNA.

Ross AE, Lawson TA
Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105
Cancer Lett; 15(3):329-334 1982

Treatment of male MRC-Wistar rats with labeled N-nitrosopyrrolidine (NPYR) and N-nitrosohexamethyleneimine (NHX) is reported. Radioactivity profiles of the 70% perchloric acid hydrolysates of liver DNA and RNA from [3H]NHX-treated rats after cation exchange are presented. The main peak is in the same numbered fraction for both DNA and RNA, and is apparently volatile, since 90% was lost on evaporation to dryness in current nitrogen. Chromatography of DNA and RNA hydrolysates on Sephadex G-10 produced similar radioactive profiles and resulted in a single major peak of volatile substance in corresponding fractions. The results contrast with the radioactive components (RC) separated by cation exchange chromatography of 1 M HCl hydrolysates of the nucleic acids from NHX-treated rats. RNA yielded five main RC. DNA had only four RC, with 5% of the radioactivity in a peak at the same elution vol as 1,6-hexane-diol. The chromatogram of the DNA mild acid hydrolysate from NPYR-treated rats had an identical feature. These results suggest that either the two nitrosamines do not interact with purines or, if purine interaction takes place, the groups attached to the purine alter their chromatographic properties to such an extent that they elute from a Sephadex G-10 column with apurinic acid. Experiments were performed to test this hypothesis and the results obtained suggest that radioactivity was still attached to the large-mol-wt apurinic acid remaining in the dialysis tubing. The data could be due to alkylation that took place only at the phosphate groups or to a metabolite produced from NHX with two active sites, capable of forming cross-links. The findings suggest that extensive phosphotriester formation and/or cross-link formation might be a feature common to DNA alkylated by alicyclic nitrosamines. (9 Refs)

35. MULTIPLE IMMUNOGLOBULIN HEAVY-CHAIN GENE TRANSCRIPTS IN ABELSON MURINE LEUKEMIA VIRUS-TRANSFORMED LYMPHOID CELL LINES.

Alt FW, Rosenberg N, Enea V, Siden E, Baltimore D
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Mol Cell Biol; 2(4):386-400 1982

The immunoglobulin heavy-chain proteins and RNAs produced by a large number of Abelson murine leukemia virus (A-MuLV) transformants were analyzed. A variety of mu (u)-related RNA species and gamma-related species were found in these cells. The productive RNAs were termed Pu-RNA; the aberrant RNAs, Au-RNAs; and the sterile RNAs, Su-RNAs. These three classes of Cu-containing RNA species in A-MuLV transformants were characterized. The data support the concept that heavy-chain allelic exclusion is a consequence of feedback control from cytoplasmic u chains and is not controlled at the DNA or RNA levels. (53 Refs)

36. STUDIES ON THE STRUCTURE OF AVIAN MYELOBLASTOSIS VIRUS (AMV) RNA. III. ELECTRON MICROSCOPIC DEFINITION OF SECONDARY STRUCTURE.

Stokrova J, Korb J, Riman J

Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 20 Prague, Czechoslovakia

Acta Virol (Praha); 26(1/2):25-32 1982

The secondary structure of avian myeloblastosis virus (AMV) RNA was characterized by electron microscopy under moderately denaturing spreading conditions. Under denaturation by aqueous 44% formamide or 77% formamide in the presence of salts, partly stretched RNA molecules with measurable double-stranded regions were observed. This approach allowed the localization from 5 to 11 regions of preserved secondary structure on AMV RNA molecules. Topographic analysis revealed a nonrandom occurrence of stable secondary structures in several prevalent regions. These regions with higher secondary structure stability revealed certain similarity to hairpin structures localized by electron microscopy on Rous sarcoma virus RNA or to highly structured regions found on this RNA by T1 ribonuclease oligonucleotide analysis. (Author abstract) (22 Refs)

37. STUDIES ON THE STRUCTURE OF AVIAN MYELOBLASTOSIS VIRUS (AMV) RNA. II. INTEGRITY OF THE RNA IN DEPENDENCE ON RNA ISOLATION AND VIRUS PROPAGATION.

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Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 160 20 Prague, Czechoslovakia

Acta Virol (Praha); 26(1/2):12-24 1982

While sedimentation analysis revealed no basic changes in the sedimentation characteristics of 60-70 S avian myeloblastosis virus (AMV) RNA isolated under different conditions from two sources, electron microscopy exhibited differences in the length distributions of this RNA. Based on the length distribution profiles, phenol extraction showed a higher degradation effect in comparison with direct gradient centrifugation of viral lysates. Proteinase K appeared to be a more suitable nuclease inhibitor than diethylpyrocarbonate during the isolation of AMV RNA. Fundamental differences between length distributions of 60-70 S RNA from plasma AMV and that from AMV propagated in cultured leukemic myeloblasts were found. Precipitation with ethanol had no effect on the length distribution of AMV RNA. Nor did storage of leukemic chicken plasma at -70 C and one thawing substantially influence the lengths of AMV RNA. The heterogeneous length distributions of 60-70 S AMV RNA molecules with preferential size-classes were independent of virus propagation and RNA isolation. The results support the idea of preferential splitting of AMV RNA at specific sites. (Author abstract) (36 Refs)

38. MOLECULAR CLONING OF A CDNA SEQUENCE ENCODING A TROPHECTODERM-SPECIFIC MARKER DURING MOUSE BLASTOCYST FORMATION.

Brulet P, Jacob F

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Proc Natl Acad Sci USA; 79(7):2328-2332 1982

A cDNA clone has been isolated from a trophoblastoma cDNA library. The mRNA complementary to this sequence directs the in vitro synthesis of proteins. The two-dimensional electrophoretic pattern of migration of these proteins is superposable to that of the trophoblastoma intermediate filament proteins recognized by monoclonal antibody (mAb) TROMA-1. This mAb had previously been shown to label trophectoderm cells but not inner cell mass cells. With a sensitive binding assay (ultrasensitive enzymatic radioimmunoassay), these in vitro synthesized proteins were recognized by mAb TROMA-1. The proteins are immunoprecipitated by an antiserum directed against trophoblastoma intermediate filament proteins and by a serum directed against a major cytoskeletal protein found in murine extraembryonic endodermal cell lines (Endo-A). The cDNA sequence detects specific mRNA(s) migrating with 18S ribosomal RNA in trophoblastoma but not in embryonal carcinoma cells. (Author abstract) (19 Refs)

39. INTRODUCTION OF RAT GROWTH HORMONE GENE INTO MOUSE FIBROBLASTS VIA A RETROVIRAL DNA VECTOR: EXPRESSION AND REGULATION.

Doehmer J, Barinaga M, Vale W, Rosenfeld MG, Verma IM, Evans RM

The Salk Inst., San Diego, CA, 92138

Proc Natl Acad Sci USA; 79(7):2268-2272 1982

We have introduced the rat growth hormone gene into mouse fibroblasts via a retroviral DNA vector. The ability of the viral DNA to induce foci in the recipient cells was used as a dominant selection marker. Several copies of rat growth hormone DNA were integrated in the mouse cells. The transformed mouse cells expressed rat growth hormone-specific mRNA and secreted mature rat growth hormone. In rat cells, the expression of this gene is regulated by glucocorticoids. We demonstrate that hormone-dependent regulation transfers with the clone and thus appears to be an intrinsic property of the gene or its RNA products. (Author abstract) (27 Refs)

40. AN SV40 DELETION MUTANT ACCUMULATES LATE TRANSCRIPTS IN A PARANUCLEAR EXTRACT.

Campos R, Villarreal LP

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Virology; 119(1):1-11 1982

We have constructed a deletion in the SV40 late region which has lost the sequences between nucleotides 226 and 656. This deletion has lost most of utilized 5' ends, leaders, all of the intervening sequence and body acceptor site for late 19 S mRNA. We show that the transcripts made by this deletion are concentrated in a paranuclear extract relative to other subcellular fractions. Furthermore, the late transcripts of the helper virus used to grow this mutant are also concentrated in the paranuclear extract. This observation leads us to speculate that these mutant transcripts may poison the RNA transport process. (Author abstract) (33 Refs)

41. DNA REPLICATION AND CELL-CYCLE PROGRESSION OF CULTURED MOUSE FM3A CELLS AFTER TREATMENT WITH 8-METHOXYPSORALEN PLUS NEAR-UV RADIATION.

Hyodo M, Fujita H, Suzuki K, Yoshino K, Matsuo I, Ohkido M
Dept. Molecular Biology, Tokai Univ. Sch. Medicine, Boseidai, Isehara-shi, Kanagawa-ken, 259-11, Japan
Mutat Res; 94(1):199-211 1982

The effect of 8-methoxypsoralen (MOP) plus near-UV radiation upon cell-cycle progression and macromolecular synthesis was investigated in cultured mouse FM3A cells. An inhibition of cell growth was observed with increasing doses of MOP plus near-UV. The minimum doses that inhibited cell growth were 0.1 ug MOP/ml plus 5 kilojoules (kJ)/square meter (m2) or 1 ug/ml plus 1 kJ/m2. Treatment with MOP (1.0 ug/ml) or near-UV (10 kJ/m2) alone had no effect upon cell growth. When cells were exposed to 1 kJ/m2 and incubated in the presence of 1.0 ug MOP/ml for up to 30 hr, cell distribution through the cell cycle did not change until after 6 hr of treatment. After 12 hr of incubation, the G1 peak became smaller. After 18 hr, more cells were shifted toward the G2 phase, while after 24 hr, most of the cells were at the G2-M peak. This profile did not change even after a prolonged incubation of 30 hr. These results indicated that treated cells were arrested at the G2-M phases. When cells were exposed to 2.5 kJ/m2 in the presence of 1.0 ug MOP/ml, the same tendency for G2-M arrest was observed, but with an increased latency. Immediately after cells were treated with 1.0 ug MOP/ml plus 1 kJ/m2 of near-UV, 3H-thymidine incorporation fell to 40% of control value with subsequent increase after 8 hr to 70%. RNA and protein synthesis were stimulated by low doses of MOP plus near UV, but inhibited by very high doses. (33 Refs)

42. BASIS FOR THE DIFFERENTIAL ACTION OF AMINONUCLEOSIDE ON NORMAL AND TRANSFORMED HUMAN FIBROBLASTS.

Albanese EA, Studzinski GP
(c/o Studzinski) Dept. Pathology, Coll. Medicine and Dentistry of New Jersey, Newark, NJ, 07103
JNCI; 68(3):407-413 1982

Acid-soluble extracts of normal human fibroblasts (IMR 90 cells) exposed to [3H]aminonucleoside of puromycin ([3H]AMS) contained larger amounts of unchanged AMS than did similar extracts of their transformed counterparts (AG 2804 cells). The radioactive compounds present in IMR 90 cells were further analyzed by sequential high-voltage paper electrophoresis, enzyme digestion, and paper chromatography. In addition to unchanged [3H]AMS, only [3H]adenosine, [3H]inosine, and [3H]adenosine monophosphate could be detected, apparently derived from [3H]adenosine present in the [3H]AMS samples added to the cultures. Consistent with the absence of metabolism of AMS in IMR 90 cells was the failure to find AMS derivatives in the RNA or DNA of these cells. The content of ribonucleoside triphosphates (rNTPs) in acid-soluble extracts of IMR 90 cells was significantly reduced by AMS treatment, and nuclei or broken cell preparations obtained from AMS-treated IMR 90 cells incorporated [3H]UTP into macromolecules at approximately control rates, when supplemented with rNTPs. These findings indicated that the reduced level of rNTPs may be responsible for the AMS-induced inhibition of RNA synthesis in normal cells. (Author abstract) (23 Refs)

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RNA TRANSCRIPTION/ SYNTHESIS

1. PARTICIPATION OF POLY(ADP-RIBOSYL)ATION IN THE DEPRESSION OF RNA SYNTHESIS CAUSED BY TREATMENT OF MOUSE LYMPHOMA CELLS WITH METHYLNITROSOUREA.

Taniguchi T, Agemori M, Kameshita I, Nishikimi M, Shizuta Y
Dept. Medical Chemistry, Kochi Medical Sch., Kochi 781-51, Japan
J Biol Chem; 257(8):4027-4030 1982

When mouse lymphoma cells (L-1210) are treated with methylnitrosourea, a DNA-damaging agent, polyadenosine diphosphoribose (poly(ADP-ribose)) synthetase activity increases five to eight-fold in 2-3 hr, while RNA polymerase activity remains constant for an initial 2 hr and then gradually decreases to 25-30% of the control level in 5 hr. Both alpha-amanitin-sensitive and -resistant RNA polymerase activities are depressed to the same degree by the treatment with methylnitrosourea. The depression in RNA synthesis is virtually prevented when the treated cells are cultured in the presence of 3-aminobenzamide, a specific inhibitor of poly(ADP-ribose) synthetase. Analyses of the RNA extracted from the cells labeled with [3H]uridine by agarose gel electrophoresis and by poly(U)-Se-

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pharose column chromatography show that the contents of ribosomal precursor RNA and poly(A)-containing RNA are both low in the methylnitrosourea-treated cells as compared with those in the untreated cells and that the reduction in the contents of these kinds of RNA is almost completely prevented by the addition of 3-aminobenzamide to the culture medium. These results suggest that the enhancement of poly(ADP-ribosyl)ation causes the decrease in both synthesis of ribosomal RNA and messenger RNA. (Author abstract) (36 Refs)

2. CORRELATION BETWEEN MEMBRANE PERMEABILITY AND INDUCTION OF ERYTHROID DIFFERENTIATION BY DMSO IN FRIEND VIRUS TRANSFORMED ERYTHROLEUKEMIA CELLS (MEETING ABSTRACT)

Dube SK, Yamane T
No affiliation given
10th International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. International Association for Comparative Research on Leukemia and Related Diseases 187 pp., 1981.

We have measured the uptake of phosphate, leucine, uridine, thymidine and deoxyglucose by FEL (Friend erythroleukemia) cells before and after induction with DMSO (dimethyl sulfoxide). The results showed a dramatic decrease in the uptake of these molecules by induced cells amounting to a drop of about 70% of the control. Our experiments on 32P phosphate incorporation in these cells showed that newly synthesized globin mRNA appears in the cytoplasm about 10 hours after addition of DMSO. To determine whether the decrease in membrane permeability temporally coincided with globin mRNA induction, we measured the uptake of phosphate, leucine, etc at hourly intervals after addition of DMSO. A very interesting duality of effect was observed. At first hour time point, there was an increase in the uptake of these molecules and this increase continued up to about 8 hours. After that time the uptake showed first signs of decrease and this was almost concomitant to the initiation of induced globin mRNA synthesis. To further strengthen the interpretation of the uptake data, we used amphotericin B, which is known to increase membrane permeability. We found that if amphotericin B and DMSO are added together, the inducing effect of DMSO is totally wiped out, ie, no globin synthesis is observed. These results, therefore, strongly argue for a correlation between decrease in membrane permeability and induction of erythroid differentiation in FVC (Friend virus complex) transformed proerythroblasts. (no Refs)

3. INHIBITION AND RECOVERY OF DNA AND RNA SYNTHESIS IN NORMAL AND TUMOUR CELLS BY SOME NITROSOUREAS.

Gorbacheva LB, Verovsky VN, Sokolova ES, Kukushkina GV
Inst. Chemical Physics, Acad. Sciences, Vorobievskoe Chausse 2B, 117977 GSP, I Moscow V-334, USSR
INSERM Symp; 19:85-96 1981

The effects of several nitrosourea (NU) derivatives on DNA synthesis by murine bone marrow and gastrointestinal mucosa and the B16 melanoma in vivo, and on RNA synthesis in L1210 leukemia cells in vivo were studied. The compounds suppressed DNA synthesis and timing of recovery in varying degrees according to the agent used. Chromatin transcriptional activity and RNA activity in L1210 cells were also altered by NU treatment. (38 Refs)

4. CHANGES IN RNA SYNTHESIS INDUCED BY N-METHYL-N-NITROSOUREA.

Mironov NM, Prikul' IV, Gorin AI, Tseitlin PI
Lab. Human Tumors, All-Union Cancer Res. Center, Moscow, USSR
Biull Eksp Biol Med; 93(3):25-27 1982

To evaluate the mechanism of the antitumor effect of nitrosoureas, the effect of N-methyl-N-nitrosourea (MNU) on RNA synthesis was studied in isolated nuclei from the liver of Wistar rats. Incubation of chromatin with MNU resulted in the decrease of RNA synthesis. The inhibitory effect of MNU was associated with the shortening of the RNA-transcripts. (10 Refs) (In RUS)

5. RECOVERY FROM INHIBITION OF TRANSCRIPTION IN GAMMA-IRRADIATED EUGLENA CELLS.

Tsushimoto G, Kikuchi T, Ishida MR
Res. Reactor Inst., Kyoto Univ., Kumatori-cho, Sennan-gun, Osaka, 590-04, Japan
Biochim Biophys Acta; 697(1):14-19 1982

Transcriptional activity was inhibited with low doses of gamma-irradiation which did not cause the death of cells, but induced the delay of cell division in the unicellular alga Euglena. The incorporation of [14C]uracil into cells was inhibited to about 50% of non-irradiated cells immediately after 3 krad irradiation. The suppressed transcriptional activity was gradually recovered after irradiation. At about 12 hr post-irradiation, the rate of incorporation of [14C]uracil recovered to that of non-irradiated cells. The synthesis of ribosomal RNA was inhibited immediately after 3 krad irradiation, but it was recovered within 12 hr after irradiation. The synthesis of cytosol ribosomal RNA precursor was more strongly inhibited than that of other cytosol ribosomal RNAs. The synthesis of cytoplasmic organelle ribosomal RNA was also inhibited and recovered after 3 krad irradiation. (Author abstract) (15 Refs)

6. MOLECULAR EVENTS BASIC TO CELLULAR RADIATION RESPONSE.

Kolodny GM
Radiology Res. Lab., Massachusetts General Hosp., Boston, MA
Molecular Events Basic to Cellular Radiation Response. Available from National Technical Information Service, Springfield, VA, as DE81027898:, 23 pp., 1981.

The initiation and control of the division process in normal cells is studied to gain insight into changes in these regards caused by x-irradiation and neoplasia. The Primer Hypothesis for eukaryotic gene regulation proposes that small molecular weight RNA acts as primer for new RNA synthesis by hybridizing with DNA and there initiating the transcription of a new RNA chain. The experiments reported here indicate that small molecular weight RNA will induce the production of new proteins. These results are consistent with the Primer Hypothesis, and demonstrate that RNA can be taken up from the media by cells in culture and can induce in vitro the production of differentiated cell products. (Author abstract)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

7. INTERFERON-DEPENDENT INDUCTION OF MRNA FOR THE MAJOR HISTOCOMPATIBILITY ANTIGENS IN HUMAN FIBROBLASTS AND LYMPHOBLASTOID CELLS.

Fellous M, Nir U, Wallach D, Merlin G, Rubinstein M, Revel M
Institut Pasteur, Paris, France
Proc Natl Acad Sci USA; 79(10,part1):3082-3086 1982

In human cells treated with interferons, there is an increase in the amount of HLA-A,B,C and beta2-microglobulin exposed on the cell surface. We have used a cloned HLA-A,B,C cDNA probe to demonstrate by molecular hybridization that this effect of interferon is preceded by a large increase in the amount of HLA mRNA in the cell. This effect was found in five different human cell lines, with purified leukocyte and fibroblast interferons. The increase in HLA mRNA is comparable in its kinetics and dose-response to the induction of (2'-5') oligo(A) synthetase mRNA by interferons. Therefore, interferons seem to activate at least two cellular genes which have different biochemical functions. (Author abstract) (51 Refs)

8. AN ADENOVIRUS AGNOGENE.

Virtanen A, Alestrom P, Persson H, Katze MG, Pettersson U
Dept. Microbiology, Biomedical Center, Univ. Uppsala, Box 581, S-751 23 Uppsala, Sweden
Nucleic Acids Res; 10(8):2539-2548 1982

The nucleotide sequence of a 550 base pairs long segment, located between map positions 21 and 22.5 in the adenovirus Type 2 genome has been determined. S1 nuclease mapping and sequence analysis of cDNA copies of adenovirus mRNA demonstrated that the established sequence includes the i-leader which is spliced to the 5'-end of certain adenovirus mRNAs. The i-leader which is 440 nucleotides long contains an open transitional reading frame which is preceded by an AUG triplet and which terminates in the third segment of the tripartite leader. A polypeptide with the same mol wt as predicted from the DNA sequence was identified by in vitro translation of mRNA which had been selected by hybridization to DNA fragments, containing sequences from the i-leader. The results thus suggest that the i-leader, unlike other adenovirus leader segments, is used for translation. (Author abstract) (27 Refs)

9. EXPRESSION OF THE GENE ENCODING THE ADENOVIRUS DNA TERMINAL PROTEIN PRECURSOR IN PRODUCTIVELY INFECTED AND TRANSFORMED CELLS.

Binger MH, Flint SJ, Rekosh DM
Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08544
J Virol; 42(2):488-501 1982

The major product of in vitro translation of early RNA prepared from H5ts125-infected cells and selected by hybridization to adenoviral DNA fragments spanning the region from 14.7 to 31.5 map units has been shown to be identical to the 87-kilodalton terminal protein precursor. A 72-to 75-kilodalton polypeptide whose mRNA can be selected by DNA from this region and made in the presence of anisomycin was indistinguishable from the 72-kilodalton single-stranded DNA-binding protein encoded by the region from 60.1 to 66.6 map units. The accumulation of cytoplasmic RNA sequences complementary to these l-strand genes under various conditions of infection and in certain lines of transformed cells has been investigated by solution hybridization of cytoplasmic RNA to the separated strands of restriction endonuclease fragments of adenoviral DNA. During the early phase, RNA sequences complementary to the region from 11.6 to 36.7 map units were present at a concentration of 10 to 60 copies per cell, regardless of the nature of the block used to inhibit viral DNA synthesis. By 24 hr after infection in the absence of any such block, sequences complementary to the regions from 11.6 to 18.2 map units (IVa2) and from 18.6 to 36.7 map units (E2B) accumulated to concentrations of 4,800 and 280 copies per cell, respectively. The ratio of cytoplasmic E2A RNA sequences to E2B RNA sequences remained close to 10:1 throughout the time period investigated. Of the transformed cell lines which retained E2B DNA sequences that were examined, only the T2C4 line expressed these sequences in cytoplasmic RNA. The implications of these observations for regulation of expression of the adenoviral early l-strand genes are discussed. (Author abstract) (73 Refs)

10. HERPESVIRUS INFECTION ALTERS THE STEADY-STATE LEVELS OF CELLULAR POLYADENYLATED RNA IN POLYOMA VIRUS-TRANSFORMED BHK CELLS.

Nakai H, Maxwell IH, Pizer LI
(c/o Pizer) Dept. Microbiology/Immunology, Univ. Colorado Sch. Medicine, Denver, CO, 80262
J Virol; 42(3):1131-1134 1982

Polyoma-transformed BHK cells are permissive for the replication of herpes simplex virus Type 1. The effect of herpes infection on the steady-state levels of bulk mRNA sequences in these cells was studied by using cDNA to polyadenylated cytoplasmic RNA from uninfected cells. The principal findings were: (i) herpes simplex virus Type 1 infection caused a pronounced reduction in the cytoplasmic levels of moderately abundant mRNAs; (ii) after infection, increased amounts of RNA complementary to the cDNA were isolated as part of the nonadenylated cytoplasmic RNA fraction. (Author abstract) (14 Refs)

11. ACCUMULATION OF SPLICED AVIAN RETROVIRUS MRNA IS INHIBITED IN S-ADENOSYLMETHIONINE-DEPLETED CHICKEN EMBRYO FIBROBLASTS.

Stoltzfus CM, Dane RW
Dept. Microbiology, Univ. Iowa, Iowa City, IA, 52242
J Virol; 42(3):918-931 1982

The synthesis and processing of B77 avian sarcoma virus RNA in infected chicken embryo fibroblasts was followed in the presence and absence of cycloleucine, a competitive inhibitor of the synthesis of S-adenosylmethionine and thus an inhibitor of RNA methylations. An increase in the steady-state levels of genome-length RNA and a decrease in the steady-state levels of subgenomic RNA molecules were obtained in the S-adenosylmethionine-depleted avian sarcoma virus-infected cells. The total number of virus-specific RNA molecules per cell, however, remained relatively constant under either condition. The production of newly synthesized virus-specific RNA in cycloleucine-treated and untreated cells infected with a transformation-defective strain of B77 avian sarcoma virus was followed as a function of [3H]uridine labeling time. The accumulation of radioactive genome-length 8.4-kilobase (kb) RNA continued in cycloleucine-treated cells, and virus particle production proceeded at normal rates. Newly synthesized 3.5-kb subgenomic mRNA, the putative mRNA for the envelope protein precursor, failed to accumulate in the treated cells. The extent of the inhibition in the appearance of the radioactive

3.5-kb RNA was correlated with the extent of the inhibition of viral genomic and cellular mRNA methylations and was a function of the cycloleucine concentration. When the accumulation of 3.5-kb envelope protein mRNA was blocked by the cycloleucine treatment, there were significant increases in the rate of synthesis of the polypeptide products of the genome-length RNA, the precursors to the non-glycosylated gag proteins and the reverse transcriptase relative to the rate of synthesis of the envelope protein precursor. These results suggest that there is an S-adenosylmethionine requirement for the splicing, but not for the synthesis, packaging, or messenger function, of avian retrovirus genome-length RNA. Possible reasons for this requirement are discussed. (47 Refs)

12. EVIDENCE FOR SIMIAN VIRUS 40 LATE TRANSCRIPTIONAL CONTROL: MIXED INFECTIONS OF WILD-TYPE SIMIAN VIRUS 40 AND A LATE LEADER DELETION MUTANT EXHIBIT TRANS EFFECTS ON LATE VIRAL RNA SYNTHESIS.

Alwine JC
Dept. Microbiology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
J Virol; 42(3):798-803 1982

Mixed infections involving equal multiplicities of wild-type simian virus 40 and viable deletion mutant dl861 resulted in decreased cytoplasmic levels of wild-type-derived late mRNA, as well as very low to undetectable levels of mutant-derived late mRNA, as compared with individual infections. The dl861 deletion removes 16 to 25 base pairs from the late leader region. This deletion was shown to be the direct cause of the mixed-infection effect; replacement of the deletion with wild-type sequences restored normal levels of late mRNAs in mixed infections. Other viral functions, eg, early gene expression and replication, were found to be unaffected by the dl861 deletion. Further examination of the mixed-infection effect showed that the levels of unspliced nuclear precursors of late mRNA, derived from both the mutant and wild-type genomes, were decreased or undetectable, in accord with the cytoplasmic results. Thus, the effect appears to be occurring at the transcriptional level. These data demonstrate a trans-acting effect on late transcription, which is detectable due to the presence of the dl861 mutant in the mixed infection. This finding is indicative of a diffusible factor which exerts a control on simian virus 40 late gene expression at the transcriptional level. A model for positive control of simian virus 40 late gene expression is presented. (Author abstract) (14 Refs)

13. KINETICS OF INDUCTION AND MOLECULAR SIZE OF MRNAS ENCODING HUMAN INTERLEUKIN-2 AND GAMMA-INTERFERON.

Efrat S, Pilo S, Kaempger R
Dept. Molecular Virology, Hebrew Univ., Hadassah Medical Sch., 91 010 Jerusalem, Israel
Nature; 297(5863):236-239 1982

In an attempt to understand the regulation of expression of interleukin-2 (IL-2) and gamma-interferon (IFN-G), a messenger RNA (mRNA) species encoding IL-2 and IFN-G was induced in mitogen-stimulated normal human lymphocytes and their expression in Xenopus laevis oocytes examined. On microinjection, distinct species of mRNA sedimenting at 10-10.5 Svedberg units (S) and 13-13.5 S directed the synthesis and secretion of active IL-2 and IFN-G, respectively. A second species IL-2 mRNA was consistently revealed, sedimenting at 13-13.5 S and comprising approx 20% of the total IL-2 mRNA activity. During induction, an initial concomitant rise in IL-2 and IFN-G mRNA activities was followed promptly by a concomitant decline in the the rate of their accumulation. (10 Refs)

14. TRANSCRIPTION OF GLOBIN GENES IN CELLS TRANSFORMED BY RAUSCHER VIRUS.

Peresleni TIu, Mechetner EB, Rozinova EN, Dvorkin GA
Inst. General Genetics, Moscow, USSR
Biokhimiia; 47(2):312-316 1982

The content of globin messenger RNA (mRNA) was studied in cultured cells of Rauscher erythroleukemia (REL) and in spleen of mice with REL. Molecular hybridization of globin complementary DNA with cytoplasmic RNA showed virtual absence of mRNA in REL cells. These findings indicate that impairment of Hb synthesis in REL is associated with the absence of mRNA and not with the impairment of its translation. (16 Refs) (In RUS)

15. TRANSITIONAL CELLULAR PHASES OF OSTEOMYELITIS TO CARCINOMA: A MORPHOLOGIC ANALYSIS.

Jaworek TE
Lawrence Park Medical Art Center, 4348 Iroquois Ave., Erie, PA, 16511
J Foot Surg; 21(2):96-100 1982

The process of development of carcinoma in osteomyelitis was followed for 14 mo in Sprague-Dawley rats with femoral osteomyelitis caused by infection with a penicillin-resistant coagulase-positive phage type 80-81 Staphylococcus aureus organism. Neoplasia could develop from inflammatory skin sinuses, which resulted from sequestrum (isolated necrotic tissue), which in turn developed from advanced suppuration and ischemia. Neoplastic cells comprised the osseus tissue parenchyma. The malignant cells were invasive and expansile, moving along lines of least resistance with contact with the stroma and underlying parenchyma. During the transition from infectious to neoplastic process ribosomes became detached and did not appear in clusters, indicating that the major filament, consisting primarily of messenger RNA, was dissolved. (6 Refs)

16. ON THE MECHANISM OF 5-BROMODEOXYURIDINE INDUCTION OF PROLACTIN SYNTHESIS IN GH CELLS (MEETING ABSTRACT)

Hanes SD, Biswas DK
Department of Pharmacology, Harvard School of Dent Med, Boston, MA, 02115
Fed Proc; 41(3):1294 1982

Treatment of prolactin-nonproducing (PRL-) substrains of GH (growth hormone) (rat pituitary tumor) cells with 5'-bromodeoxyuridine (BrdUrd) induces prolactin (PRL) synthesis in these cells. Induction of PRL synthesis can be correlated with concomitant increased levels of cytoplasmic translatable and cDNAPRL hybridizable RNAPRL sequences. Analysis of nuclear RNAPRL sequences revealed several RNA species of approximately 25-30S, 18-19S and 12-13S. Only the 12-13S RNA species could be detected in the cytoplasmic poly(A) RNA fraction. Elevated levels of both nuclear and cytoplasmic RNAPRL sequences are observed after BrdUrd treatment of these GH cell substrains. These results suggest that BrdUrd induction of PRL synthesis in PRL-strains is mediated via transcriptional steps. The molecular mechanism/s involved in such stimulation of transcription in relation to the regulation of expression of specific genes in eukaryotic cells has been probed into and these results will be presented. (no Refs)

17. EXPRESSION AND MOLECULAR SIZE OF MESSENGER RNA SPECIES ENCODING INTERLEUKIN-2 AND GAMMA INTERFERON FROM NORMAL HUMAN LYMPHOCYTES (MEETING ABSTRACT)

Kaempfer R, Efrat S, Pilo S
The Hebrew University-Hadassah Medical School, 91 010 Jerusalem, Israel
Fed Proc; 41(3):957 1982

Cultivation of lymphocytes from freshly excised human tonsils in the presence of PHA (phytohemagglutinin), with or without 12-O-tetradecanoylphorbol 13-acetate (TPA), led to production and secretion of interleukin-2 (IL-2) and gamma interferon (gamma-IFN). Total RNA extracted from such cells was purified and fractionated by two cycles of oligo (dT)-cellulose chromatography and by sucrose gradient centrifugation after heating in the presence of dimethylsulfoxide. Upon microinjection into Xenopus laevis oocytes, a peak of mRNA sedimenting at 11 S directed the extensive synthesis and secretion of active IL-2, as assayed by stimulation of DNA synthesis in T-cell growth factor-dependent human lymphocyte cell lines. The IL-2 mRNA sedimented ahead of globin mRNA, whose expression was monitored in a reticulocyte lysate, but behind a sharp 13 S peak of mRNA that directed, upon microinjection into oocytes, the extensive synthesis and secretion of active gamma-IFN, as assayed by pH 2-sensitive protection of a human amnion cell line against the cytopathic effect of Mengovirus. A second peak of IL-2 mRNA was consistently revealed, sedimenting at 13 S, that comprised about 20% of the total IL-2 mRNA activity. The ratio of 11 S to 13 S IL-2 mRNA species was not affected by TPA, but this tumor promoter considerably raised the specific activity of the IL-2 mRNA. (no Refs)

18. SYNTHESIS AND TURNOVER OF REGULATORY SUBUNIT OF PROTEIN KINASE I IN NEUROBLASTOMA CELLS (MEETING ABSTRACT)

Prashad N
Graduate School of Biomedical Sciences, University of Texas Health Science Center, Houston, TX, 77025
Fed Proc; 41(3):659 1982

Multiple forms of a regulatory subunit of PKI (R1 and R) exist in mouse neuroblastoma cells. R1 and R have a MW of 48,000; however, the pI are different, R1 (PI 5.2) and R (PI 5.4). DibutyrylcAMP increased R by 3-fold without affecting R1. Pulse labeling of cells with 35(s)met for 5 min, show an increase in R by 2-fold in dibutyrylcAMP treated cells compared to control cells, suggesting increase in R is due to de novo synthesis. Translation of 1ug of poly(A)+RNA in reticsys show a 2-fold increase in the synthesis of R by poly(A)+RNA from dibutyrylcAMP treated cells compared to control cells. These results indicate dibutyrylcAMP-induced R is due to increase in the specific mRNA, suggesting different mechanisms for the synthesis of R1 and R. The turnover rates of R1 and R were determined by chasing 35(S)met labeled cells in the absence and presence of dibutyrylcAMP. The half-life of R in the absence of dibutyrylcAMP was 25 hr and in the presence of dibutyrylcAMP R was stabilized, decreasing 16% after 48 hr. In contrast, R1 was stable in the absence or presence of dibutyrylcAMP, decreased by 23% after 48 hr. These data show R1 and R have different turnover rates. Therefore, dibutyrylcAMP induced R, due to increased synthesis as well as increased stability due to R-cAMP complex formation. Characterization and understanding the functions of multiple forms of regulatory subunit will help to understand their role in cellular functions, especially in dibutyrylcAMP-induced differentiation. (no Refs)

19. MULTIPLE GAMMA-CRYSTALLINS OF THE MOUSE LENS: FRACTIONATION OF MRNAS BY CDNA CLONING.

Shinohara T, Robinson EA, Appella E, Piatigorsky J
(c/o Piatigorsky) Lab. Molecular and Developmental Biology, Natl. Eye Inst., Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(9):2783-2787 1982

The cDNAs made from polyadenylated RNAs of the mouse lens were cloned by the G-C tailing procedure in the bacterial plasmid pBR322. Four recombinant DNAs containing gamma-crystallin sequences were identified by hybrid selection and translation. Sequence analysis of the in vivo-labeled gamma-crystallin polypeptides that cofocused isoelectrically with the hybrid-selected translation products established that the four cloned cDNAs were derived from mRNAs encoding gamma-crystallin polypeptides with similar NH2 termini. The cDNA clones had different restriction maps and could discriminate among the different gamma-crystallin mRNAs under stringent hybridization conditions. Under relaxed hybridization conditions, the cDNA clones cross-hybridized with all gamma-crystallin mRNAs, and even slightly with beta-crystallin mRNAs, as judged by in vitro translation. RNA blot hybridization showed that the mouse lens gamma-crystallin mRNAs are 840 +-100 nucleotides long. These data indicate that there are at least four similar gamma-crystallin mRNAs and suggest (but do not establish) the existence of a closely related family of gamma-crystallin genes. (Author abstract) (35 Refs)

20. EXPRESSION AND METHYLATION OF THE MOUSE ALPHA-FETOPROTEIN GENE IN EMBRYONIC, ADULT, AND NEOPLASTIC TISSUES.

Andrews GK, Dziadek M, Tamaoki T
Dept. Medical Biochemistry, Faculty Medicine, Univ. Calgary, Calgary, Alberta, T2N 4N1, Canada
J Biol Chem; 257(9):5148-5153 1982

Expression of the mouse alpha-fetoprotein gene in embryonic, adult, and neoplastic tissues was assessed by RNA dot hybridization using 32P-labeled alpha-fetoprotein cDNA as probe. Alpha-fetoprotein mRNA was present in high levels in total RNA from yolk sac endoderm, fetal liver, and an alpha-fetoprotein-producing hepatoma. In contrast, this mRNA was greatly depleted in total RNA from yolk sac mesoderm and essentially absent in brain, adult liver, and a non-alpha-fetoprotein-producing hepatoma. These results indicated that alpha-fetoprotein gene expression was controlled primarily at the transcriptional level. The presence of the modified base, 5-methylcytosine, in the alpha-fetoprotein gene was studied by comparing hybridization patterns obtained by Southern blot analysis of DNA cleaved with the restriction isoschizomers endonuclease Msp I and endonuclease Hpa II. The gross sequence organization and reiteration frequency of the alpha-fetoprotein gene were invariant among the DNA samples, whereas, in each case, there was a positive correlation between hypomethylation of six CCGG (Hpa II) sites in the alpha-fetoprotein gene and expression of this gene. These Hpa II sites were distributed throughout a large portion of the alpha-fetoprotein gene. Patterns of cytosine methylation in this gene were established before day 15 of gestation in yolk sac endoderm and mesoderm. (Author abstract) (46 Refs)

21. NUCLEOTIDE SEQUENCE SURROUNDING MULTIPLE POLYADENYLATION SITES IN THE MOUSE DIHYDROFOLATE REDUCTASE GENE.

Setzer DR, McGrogan M, Schimke RT
Dept. Embryology, Carnegie Inst. Washington, Baltimore, MD, 21210
J Biol Chem; 257(9):5143-5147 1982

We have previously reported the presence of four dihydrofolate reductase messenger RNAs differing in the length of 3' untranslated regions in murine cells. We have now mapped the 3' ends of these RNAs more precisely and have demonstrated colinearity between their shared sequences. Analysis of three larger dihydrofolate reductase RNAs has shown that these RNA species contain very long 3' noncoding regions, bringing the total number of dihydrofolate reductase RNAs to seven, ranging in length from 750 to 5,600 nucleotides. We have determined the nucleotide sequence at and surrounding the polyadenylation sites of the four smaller RNAs. We find no striking structures in this sequence that might constitute multiple polyadenylation signals, but conclude that the putative polyadenylation signal AAUAAA is not required for polyadenylation of at least three of the four dehydrofolate reductase messengers. (Author abstract) (22 Refs)

22. SYNTHESIS OF HUMAN ADENOVIRUS EARLY RNA SPECIES IS SIMILAR IN PRODUCTIVE AND ABORTIVE INFECTIONS OF MONKEY AND HUMAN CELLS.

Anderson KP, Klessig DF
Dept. Cellular, Viral, and Molecular Biology, Univ. Utah, Salt Lake City, UT, 84132
J Virol; 42(2):748-754 1982

Northern (RNA) blot analysis has been used to show that synthesis of early mRNA species is similar in monkey cells productively or abortively infected with human adenovirus. mRNA species from all five major early regions (1A, 1B, 2, 3, 4) are identical in size and comparable in abundance whether isolated from monkey cells infected with adenovirus Type 2 or with the host range mutant Ad2hr400 or coinfected with adenovirus Type 2 plus simian virus 40. The mRNA species isolated from monkey cells are identical in size to those isolated from human cells. Production of virus-associated RNA is also identical in productive and abortive infections of monkey cells. Synthesis of virus-associated RNA is, however, significantly greater in HeLa cells than in CV1 cells at late times after infection regardless of which virus is used in the infection. (Author abstract) (36 Refs)

STRUCTURE AND LEVELS OF RIBOSOMAL RNA

23. HUMAN RIBOSOMAL RNA GENE: NUCLEOTIDE SEQUENCE OF THE TRANSCRIPTION INITIATION REGION AND COMPARISON OF THREE MAMMALIAN GENES.

Financsek I, Mizumoto K, Mishima Y, Muramatsu M
Dept. Biochemistry, Cancer Inst., Japanese Foundation for Cancer Res., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan
Proc Natl Acad Sci USA; 79(10,part1):3092-3096 1982

The transcription initiation site of the human ribosomal RNA gene (rDNA) was located by using the single-strand specific nuclease protection method and by determining the first nucleotide of the in vitro capped 45S preribosomal RNA. The sequence of 1,211 nucleotides surrounding the initiation site was determined. The sequenced region was found to consist of 75% G and C and to contain a number of short direct and inverted repeats and palindromes. By comparison of the corresponding initiation regions of three mammalian species, several conserved sequences were found upstream and downstream from the transcription starting point. Two short A + T-rich sequences are present on human, mouse, and rat ribosomal RNA genes between the initiation site and 40 nucleotides upstream, and a C + T cluster is located at a position around-60. At and downstream from the initiation site, a common sequence, T-G/A-C-T-G-A-C-A-C-G-C-T-G-T-C-C-T-T/C-T, was found in the three genes from position-1 through +18. The strong conservation of these sequences suggests their functional significance in rDNA. The S1 nuclease protection experiments with cloned rDNA fragments indicated the presence in human 45S RNA of molecules several hundred nucleotides shorter than the supposed primary transcript. The first 19 nucleotides of these molecules appear identical - except for one mismatch - to the nucleotide sequence of the 5' end of a supposed early processing product of the mouse 45S RNA. (Author abstract) (43 Refs)

STRUCTURE AND LEVELS OF TRANSFER RNA

24. LOSS OF TRNA 5-METHYLURIDINE METHYLTRANSFERASE AND PSEUDOURIDINE SYNTHETASE ACTIVITIES IN 5-FLUOROURACIL AND 1-(TETRAHYDRO-2-FURANYL)-5-FLUOROURACIL (FTORAFUR)-TREATED ESCHERICHIA COLI.

Frendewey DA, Kladianos DM, Moore VG, Kaiser II
(c/o Kaiser) Dept. Biochemistry, Univ. Wyoming, Laramie, WY, 82071
Biochim Biophys Acta; 697(1):31-40 1982

Transfer-RNAs from Escherichia coli B treated with either 5-fluorouracil or its analog, 1-(tetrahydro-2-furanyl)-5-fluorouracil (ftorafur), contain low levels of 5-fluorouracil, but are grossly deficient in pseudouridine and 5-methyluridine. The enzymes responsible for the formation of these two modified nucleosides, tRNA pseudouridine synthetase and (5-methyluridine)-methyltransferase, show substantially reduced activity levels in extracts from ftorafur- and 5-fluorouracil-treated cells relative to preparations from normal cells. When these tRNA-modifying activities are examined in vitro, both are inhibited by the addition of fluorouridine-containing tRNAs to the reaction mixtures. Pseudouridine synthetase activity shows potent inhibition. These inhibitory properties of fluorouridine-containing tRNAs, plus the inability of tRNA (5-methyluridine)-methyltransferase to efficiently use fluorouridine-containing tRNAs as substrates, appear to account for the deficiency of 5-methyluridine and pseudouridine in tRNAs from cells containing low levels of 5-fluorouracil. (Author abstract) (44 Refs)

25. NUCLEOTIDE SEQUENCE ANALYSIS OF THE LONG TERMINAL REPEAT OF INTEGRATED SIMIAN SARCOMA VIRUS: EVOLUTIONARY RELATIONSHIP WITH OTHER MAMMALIAN RETROVIRAL LONG TERMINAL REPEATS.

Devare SG, Reddy EP, Law JD, Aaronson SA
Lab. Cellular and Molecular Biology, NCI, Bethesda, MD, 20205
J Virol; 42(3):1108-1113 1982

Nucleotide sequence analysis of the long terminal repeat (LTR) of the integrated simian sarcoma virus showed that the simian sarcoma virus LTR comprised 504 nucleotides with an inverted repeat of seven bases at its 5' and 3' termini. At the site of simian sarcoma virus integration, cellular flanking sequences adjacent to the proviral LTR contained a direct repeat of four bases. A 13-base sequence after the 5' LTR was found to be complementary to prolyl tRNA, suggesting that tRNA-Pro may serve as the primer for reverse transcription of simian sarcoma virus RNA. The U5 and R regions, derived respectively from the 5' end and terminally redundant sequences of the viral RNA, were found to have similar organization and sequence homology close to that of Moloney murine sarcoma virus or Moloney murine leukemia virus. These results indicate that regions within LTRs with known functionally important sequences have been most well conserved during retrovirus evolution. (Author abstract) (45 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

26. SYNTHESIS OF (2'-5')OLIGOADENYLATE AND ACTIVATION OF AN ENDORIBONUCLEASE IN INTERFERON-TREATED HELA CELLS INFECTED WITH REOVIRUS.

Nilsen TW, Maroney PA, Baglioni C
(c/o Baglioni) Dept. Biological Sciences, State Univ. New York at Albany, Albany, NY, 12222
J Virol; 42(3):1039-1045 1982

Treatment with interferon protected HeLa cells from infection with reovirus. This virus apparently activated an antiviral mechanism that was detected by the presence of (2'-5')oligoadenylate [(2'-5')An] in intact cells. The (2'-5')An was previously shown to activate an endoribonuclease, RNase L. We measured (2'-5')An by a sensitive competition-binding assay in cells infected at different multiplicities and for different lengths of time. Nanomolar concentrations of (2'-5')An were detected in cells infected at a multiplicity of greater than 5 after 2 hr of infection, the time at which the infecting virions were uncoated. The level of (2'-5')An increased up to 6 hr postinfection but declined afterward. To establish whether viral mRNAs were cleaved by RNase L, we analyzed the RNA extracted from infected cells by a highly specific hybridization assay on Northern blots. Full-sized reovirus mRNAs were detected in control infected cells, but not in interferon-treated infected cells, at 6 hr postinfection. At this time, a nuclease activity could be detected in these cells by demonstration of cleavage of rRNA, degradation of cellular mRNA, and polysome breakdown in the presence of emetine. Since this inhibitor freezes ribosomes, cleavage of mRNA between ribosomes could only be accounted for by an endonuclease, presumably RNase L. (Author abstract) (24 Refs)

27. CONTROL OF THE PPP(A2'P)NA SYSTEM IN HELA CELLS. EFFECTS OF INTERFERON AND VIRUS INFECTION.

Silverman RH, Cayley PJ, Knight M, Gilbert CS, Kerr IM
Dept. Pathology, Uniformed Services Univ. Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20205
Eur J Biochem; 124(1):131-138 1982

HeLa cells have an unusually high level of ppp(A2'p)nA synthetase (n = 2 to greater than or equal to 4) even in the absence of interferon treatment. In accord with this ppp(A2'p)nA and ppp(A2'p)nA-mediated ribosomal RNA cleavage occur naturally in response to encephalomyocarditis virus infection in control as well as in interferon-treated cells. Despite this, in the absence of interferon treatment, encephalomyocarditis virus grows well in these cells. A possible explanation for this paradox is that the ppp(A2'p)nA dependent RNase is lost or inactivated at later times post-infection in control but not in interferon-treated cells. It appears, therefore, to be the prevention by interferon of the virus-mediated inhibition of the ppp(A2'p)n-dependent nuclease rather than the absolute level or induction of the ppp(A2'p)nA synthetase which is crucial for the activity of the ppp(A2'p)nA system in HeLa cells. These results provide evidence for a further level of control in the ppp(A2'p)nA system and show that limited ppp(A2'p)nA-mediated ribosomal RNA cleavage alone is not sufficient to cause an inhibition of virus growth. (Author abstract) (33 Refs)

28. CORRELATION OF ESTROGEN RECEPTOR LEVELS WITH DNA-DEPENDENT RNA POLYMERASE ACTIVITY IN 7,12-DIMETHYL BENZ(A)ANTHRACENE (DMBA)-INDUCED MAMMARY TUMORS IN RATS (MEETING ABSTRACT)

Hunter JB, Mohla S
Department of Oncology and Pharmacology, Howard University Cancer Center, Washington, DC, 20060
Med Pediatr Oncol; 10(1):101 1982

Approximately 60% of breast cancer patients have estrogen receptors (ER) of which two thirds respond favorably to hormonal therapy. Estrogens act on their target tissues by interacting with their cytoplasmic receptors, followed by translocation of the estrogen receptor complex into the nucleus. This results in increased RNA synthesis as evidenced by increased RNA polymerase activity. Using DMBA-induced mammary tumors in rats, experiments were designed to see whether RNA polymerase activity of isolated tumor nuclei may be related to their cytoplasmic ER levels. Mammary tumors were induced by a single intragastric feeding of 15 mg DMBA in 1.5 ml peanut oil. Mammary tumors were analyzed for ER using dextran coated charcoal or sucrose density gradient methods. Tumor nuclei were isolated using fresh, minced tissue and analyzed for RNA polymerase activity as previously described. Seventyseven percent (10/13) of ER positive greater than 10 femto moles/mg protein) tumors exhibited low RNA polymerase activity (less than 200 pico moles of 3H-UMP/mg DNA). In contrast 83% (5/6) of ER negative (less than 10 femto moles/mg protein) tumors showed high RNA polymerase activity (greater than 200 pico moles of 3H-UMP/mg DNA). Similarly, the incorporation of 3H-AMP into RNA was lower (less than 200 pico moles/mg DNA) in 91% (10/11) of ER positive tumors, whereas the majority of ER negative tumors (63%) showed higher (greater than 200 pico moles/mg DNA) 3H-AMP incorporation. The incorporation of 3H-GMP into RNA also exhibited a similar correlation to ER. These data suggest additional biochemical parameters to distinguish between ER positive and ER negative tumors. (1 Ref)

29. 5-MERCAPTOPOLYURIDYLIC ACID (MPU), A POTENT INHIBITOR OF THE REVERSE TRANSCRIPTASE FROM AVIAN MYELOBLASTOSIS VIRUS.

Kung MP, Ho YK, Bardos TJ
Dept. Biochemical Pharmacology, Biophysical Sciences, State Univ. New York at Buffalo, Buffalo, NY, 14260
Res Commun Chem Pathol Pharmacol; 36(2):215-228 1982

The effects of partially thiolated polyuridylic acid (MPU), partially thiolated polycytidylic acid (MPC), and their unmodified counterparts, poly(U) and poly(C), respectively, on the reverse transcriptase of avian myeloblastosis virus (AMV) have been determined, using different temperature-primers. Poly(C) stimulated and MPC inhibited the polymerization reaction catalyzed by the AMV reverse transcriptase in the presence of the natural viral template (endogenous RNA or purified 70S RNA), or with poly(C)-oligo(dG)12-18 but not with poly(A)-oligo(dT)12-18 as the only template-primer present in the purified enzyme system. Both poly(U) and MPU inhibited the reaction in the presence of either of the synthetic or natural templates. Using the purified enzyme with the 70S RNA template, MPU was by far the most potent inhibitor, with I50 = 0.8 uM based on the epsilon(P) value, or I50 less than 3 x 10(-9) M based on the actual, macromolecular weight of the polynucleotide. (Author abstract) (29 Refs)

OTHER RELATED STUDIES

30. EXPRESSION OF ADENOVIRAL GENETIC INFORMATION IN PRODUCTIVELY INFECTED CELLS.

Flint SJ
Dept. Biochemical Sciences, Princeton Univ., Princeton, NJ, 08544
Biochim Biophys Acta; 651(2/3):175-208 1982

Recent advances in the understanding of mechanisms and regulation of adenoviral gene expression are reviewed. Topics discussed include the structure of adenoviral early genes (early regions E1-E4 and expression of additional genes during early phase of infection), synthesis of adenoviral early messenger RNA species, regulation of adenoviral early gene expression, organization and expression of adenoviral late genes, the early to late transition, structure and function of adenoviral 'promoter' sites, and the virus associated (VA)-RNA genes. (225 Refs)

31. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

Rajalakshmi S, Prema M, Sarma D
Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The nature of modified nucleic acids following interactions with carcinogens is reviewed. Interactions of chemical carcinogens with DNA include covalent interactions such as alkylating agents, nitrosamines and nitrosamides, and noncovalent interactions of both internal and external binding types. Purine-N-oxides and many inorganic metal compounds are known to be carcinogenic. The use of fractionation techniques has revealed that carcinogens exhibit a preferential interaction with some regions of DNA in chromatin. Interactions of chemical carcinogens with RNA have been studied, and alterations in RNA have been attributed to alkylating agents such as nitrosamines and nitrosamides, to urethan, to aromatic amines and amides, and to polycyclic aromatic hydrocarbons. Interactions of carcinogens with nucleic acids exert a profound effect on the structure and synthesis of DNA and RNA, gene expression, and regulation of cellular development. Although the exact mechanism or mechanisms by which DNA damage and repair are involved in carcinogenesis is not completely understood, there is overwhelming evidence indicating a causal relationship between these two processes. (634 Refs)

32. ISOLATION AND CHARACTERIZATION OF C-MYC, A CELLULAR HOMOLOG OF THE ONCOGENE (V-MYC) OF AVIAN MYELOCYTOMATOSIS VIRUS STRAIN 29.

Vennstrom B, Sheiness D, Zabielski J, Bishop JM
Dept. Microbiology, Univ. Uppsala, Biomedical Center, Uppsala, Sweden
J Virol; 42(3):773-779 1982

The chicken genome contains nucleotide sequences homologous to the transforming genes (oncogenes) of a number of avian retroviruses. We have isolated chicken DNA (c-myc) that is homologous to the oncogene (v-myc) of the avian myelocytomatosis virus MC29 and have compared the structures of the cellular and viral genes. Results from restriction endonuclease mapping of c-myc and from analysis of heteroduplexes between the DNAs of the cellular and viral genes show that c-myc is homologous to 1,500 nucleotides in v-myc DNA. This homologous region is interrupted in c-myc by an intron-like sequence of 1,100 nucleotides which is absent from v-myc. Nuclear RNA from normal chicken cells contains at least five species of transcripts from c-myc ranging from 2.5 to 6.5 kilobases in length. By contrast, cytoplasm contains only the 2.5-kilobase c-myc RNA. These features of the c-myc gene and its nuclear transcripts are characteristic of normal cellular genes and suggest that the myc gene is of cellular rather than viral origin. The exons in c-myc may define two functional domains in the gene and may therefore facilitate the dissection of the different oncogenic potentials of the MC29 virus. (Author abstract) (28 Refs)

33. SUPPRESSION OF SPONTANEOUS MAMMARY TUMORIGENESIS DESPITE MTV-1 GENE EXPRESSION IN HYBRID AND BACKCROSS C3H-AVYFB X C3H/SM MICE.

Smith GH, Henry TJ, Vlahakis G, Arthur LO
Lab. Molecular Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(5):591-598 1982

Mouse mammary tumor virus (MMTV)-specific RNA and antigen content of normal and neoplastic mouse mammary tissue were measured in strains C3H/Sm and C3H-AvyfB in C3H-AvyfB female x C3H/Sm male F1 hybrids and in (C3H-AvyfB x C3H/Sm) x C3H/Sm male backcross segregants. The molecular data, along with the relative mammary tumor incidences, suggest that the endogenous MMTV provirus expression gene Mtv-1 present in C3H mice is fully expressed in the C3H-AvyfB subline but is silent or more probably absent in the C3H/Sm subline. Cessation of translational expression of endogenous MMTV occurred only in the agouti backcross females, suggesting an association between this phenomenon and the agouti locus of C3H/Sm. Evaluation of the relative MMTV RNA content of nucleic and cytoplasmic fractions from C3H/Sm mammary tissues strongly suggests that transport and/or processing of MMTV RNA is defective in these mice. This defect probably accounts for the absence of detectable MMTV antigens in C3H/Sm and agouti backcross mammary tissues and tumors and may contribute to the observed reduction in mammary tumor incidence. (27 Refs)

34. METABOLISM OF FAST LABELING NUCLEAR RNA IN SPLEEN CELLS OF MICE WITH RAUSCHER LEUKEMIA.

Smirnova IA, Kishinskaia EG
R. E. Kavetskii Inst. Problem Oncology, Kiev, USSR
Ukr Biokhim Zh; 54(2):159-162 1982

Synthesis and degradation of fast labeling RNA with sedimentation coefficient of 35 Svedberg (S) were studied in splenocytes from BALB/c mice infected with Rauscher leukemia virus (RLV). The 35 S RNA was characterized by a higher metabolic activity than other RNA fractions in leukemic cells. Molecular hybridization showed that 35 S RNA consisted of the sequences which were complementary to RLV genome and to the cell genome. (10 Refs) (In RUS)

35. NUCLEOTIDE SEQUENCE OF 7 S RNA. HOMOLOGY TO ALU DNA AND LA 4.5 S RNA.

Li WY, Reddy R, Henning D, Epstein P, Busch H
Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
J Biol Chem; 257(9):5136-5142 1982

The 7 S RNA component, a part of normal higher eukaryotic cells and several oncornaviruses, was shown to be conserved in evolution. Recently, 7 S RNA was shown to be partially complementary to Alu family DNA sequences. In the present study the nucleotide sequence of Novikoff hepatoma 7 S RNA was determined. Comparison of 7 S RNA, Alu and B1 family DNA, and La 4.5 S RNA sequences for homologies showed that (1) one-third of 7 S RNA, mainly the 5'-end, was homologous to Alu and B1 family sequences; (2) one 300-nucleotide long Alu family sequence contained two binding sites for 7 S RNA; and (3) the 5'-ends of 7 S RNA and La 4.5 S RNA also had extensive (60%) homologies. A model for the secondary structure of 7 S RNA based on maximal base pairing and preferential nuclease cleavage sites is also presented. (33 Refs)

36. EFFECTS OF METHOTREXATE ON RIBONUCLEOTIDE POOLS IN GROWING AND IN GROWTH-ARRESTED TUMOR CELLS AND ANTAGONISM BY RNA SYNTHESIS INHIBITORS.

Kaminskas E
Dept. Medicine, Hebrew Rehabilitation Center for Aged, Harvard Medical Sch., 1200 Centre St., Boston, MA, 02131
J Biol Chem; 257(8):4279-4284 1982

We examined the mechanism of ribonucleotide pool changes in methotrexate-treated Ehrlich ascites tumor cells in culture. In exponentially growing cells, methotrexate inhibited ATP and GTP formation and stimulated UTP and CTP formation by the de novo pathways. Over the following 4 hr ATP and GTP decreased and UTP and CTP increased. During this period RNA synthesis rates decreased by 30 to 40%. Inhibitors of nucleolar RNA synthesis (actinomycin D, doxorubicin, or cycloheximide), but not of DNA synthesis (cytosine arabinoside), prevented ATP and GTP depletion. These results suggest that ATP and GTP were depleted in methotrexate-treated cells because the shift-down of RNA synthesis occurred more slowly than the inhibition of ATP and GTP supply. UTP and CTP pools increased because of increased de novo synthesis and because of decreased consumption in RNA synthesis. Ribonucleoside triphosphates were increased and their syntheses by de novo pathways were inhibited in cells treated with RNA synthesis inhibitors. ATP decreased slightly and GTP remained unchanged in growth-arrested cells treated with methotrexate. In growth-arrested cells, de novo purine nucleotide synthesis was inhibited less and RNA synthesis rates were lower than in growing cells. (Author abstract) (45 Refs)

37. HERPES SIMPLEX VIRUS-INDUCED CHANGES IN CELLULAR AND ADENOVIRUS RNA METABOLISM IN AN ADENOVIRUS TYPE 5-TRANSFORMED HUMAN CELL LINE.

Stenberg RM, Pizer LI
(c/o Pizer) Dept. Microbiology, Univ. Colorado Medical Sch., Denver-ity, CO, 80262
J Virol; 42(2):474-487 1982

We used the viral transcripts (designated Ad-RNA) that accumulated in the cytoplasm of adenovirus Type 5-transformed human embryonic kidney cells (cell line 293-31) as models for cellular RNAs to examine how herpes simplex virus modifies cellular RNA metabolism. Infection of 293-31 cells with herpes simplex virus Type 1 Strain 17 led to extensive inhibition of Ad-RNA accumulation by 4 hr postinfection. The major part of this inhibition was due to an immediate early or alpha gene function, which reduced the rate of transcription of Ad-RNA within the nuclei of the infected cells. In addition, host polyadenylic acid-containing RNA accumulation and rRNA accumulation were affected, but to a lesser extent and at a slower rate than Ad-RNA accumulation. In conjunction with previous data, our experimental data allowed us to propose a general scheme for how herpes simplex virus Type 1 alters the metabolism of cellular RNA, the possible mechanisms for these changes, and how they correlate with the regulation of herpes simplex virus gene expression. (Author abstract) (52 Refs)

38. SYNTHESIS AND SECRETION OF RNA IN EHRLICH TUMOR CELLS.

Agliullina DG, Vegner EO, Vinter VG
State Univ., Kazan, USSR
Eksp Onkol; 4(2):38-40 1982

Synthesis and degradation of RNA in the ascites fluid of Ehrlich ascites carcinoma (EAC) was studied. Random-bred albino mice bearing EAC were inoculated ip with 3H-uracil. Within different time periods after label administration, animals were sacrificed, and RNA content in the ascites fluid was determined. Specific radioactivity of the extracellular RNA reached the max 6-9 hr after label administration. Analysis of RNA degradation after actinomycin D administration showed that the half-life of extracellular RNA was 4 hr. (14 Refs) (In RUS)

39. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.

Hochhauser SJ, Stein GS, Stein JL
Dept. Biochemistry and Molecular Biology, Univ. Florida, Coll. Medicine, Gainsville, FL, 32610
Pathobiol Annu; 11:1-29 1981

Properties of the eukaryotic genome are discussed focusing on those aspects which have a direct bearing on organization, structure, and function. The levels at which gene expression is regulated and approaches that are being taken to examine control of transcription and subsequent processing and translation of gene transcripts are reviewed. The nature of gene expression in aberrant biological situations are assessed with the objective of defining possible molecular lesions. Enzyme components of nonhistone chromosomal proteins and differences between transformed or tumorigenic and untransformed cells are summarized. (352 Refs)

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RNA

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RNA TRANSCRIPTION/ SYNTHESIS

1. DIFFERENTIAL INHIBITION OF TRANSCRIPTION OF DNA BY MELANOMA CHROMOSOMAL PROTEINS.

Lambert MW, McGuire J
Dept. Pathology, UMDNJ-New Jersey Medical Sch., 100 Bergen St., Newark, NJ, 07103

J Invest Dermatol; 78(6):498-502 1982

Histones and four nuclear nonhistone protein fractions (NHP1-4) were extracted from nuclei of a Cloudman mouse melanoma cell line (NCTC 3960, CCL 53) and tested for their ability to bind to DNA and influence transcription. The histones and NHP fractions showed different binding affinities for DNA, with the histones and NHP1 exhibiting the highest affinity. The NHP fractions differentially affected both the rate of RNA synthesis and the size of RNA transcribed. NHP1 which inhibited RNA synthesis to the greatest extent, inhibited synthesis of all sizes of RNA except for major peaks of 28S and 8S RNA and discrete minor peaks of 7S, 6S, 5S, and 4S RNA. Histones markedly enhanced the effect of NHP1 on RNA synthesis. These results suggest that there are nonhistone proteins in Cloudman melanoma nuclei which have a high affinity for

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DNA and which may be involved in the regulation of transcription. (Author abstract) (37 Refs)

2. VARIETY IN THE LEVEL OF GENE CONTROL IN EUKARYOTIC CELLS.

Darnell JE
Rockefeller Univ., New York, NY, 10021
Nature; 297(5865):365-371 1982

In light of present progress in the understanding of how messenger RNA is constructed in eukaryotic cells, the levels of gene control are discussed. Transcriptional control, assessed by the rate of synthesis of specific nuclear RNA, is strongly indicated to be the most frequent level of control. Definition of eukaryotic transcription units as simple (encoding 1 protein) and complex (encoding 2 or more proteins) affords a framework in which to discuss control at the level of RNA processing for which several examples also are known. Finally, differential stability of cytoplasmic mRNAs and differential translation, both well established, are briefly described. (Author abstract) (151 Refs)

3. BOVINE PAPILLOMA VIRUS TRANSCRIPTION: POLYADENYLATED RNA SPECIES AND ASSESSMENT OF THE DIRECTION OF TRANSCRIPTION.

Amtmann E, Sauer G
(c/o Sauer) Inst. Virus Res., German Cancer Res. Center, 6900 Heidelberg, W. Germany
J Virol; 43(1):59-66 1982

The bovine papilloma virus Type 1 (BPV-1)-specific RNA species were identified in virus-induced bovine warts, hamster tumors, and transformed hamster and mouse cells. In each case two major species were present (1.1 and 1.3 kilobases [kb]). Also two species of 1.6 and 1.8 kb appearing in variable amounts were found. Only in the keratinized periphery of the warts, where virus replication takes place, was it possible to reveal an additional 2-kb RNA species. In this tissue, however, the 1.6-kb species was not detected. The basal part of a bovine wart contained an additional minor, 2.9-kb, BPV-1-specific RNA sequence. By hybridization with purified defined BPV-1 DNA fragments it was shown that most of the coding sequences of the 2-kb species were transcribed from a region between 0.02 and 0.19 map units. The majority of the coding sequences of the smaller species in transformed cells were located in the region between 0.31 and 0.61 map units. The putative 5' ends mapped between 0.72 and 0.96 map units. Oligodeoxythymidylic acid-primed [32P]cDNA was synthesized from various RNA preparations to generate probes for the detection of 3' termini of the polyadenylated BPV-1 RNAs. By hybridization across the BPV-1 genome only one signal between the map positions 0.30 and 0.40 was obtained when RNA from transformed cells and from a tumor was used as a template. In contrast, RNA from the periphery of a wart led to the detection of an additional signal which was confined to the region between 0.96 and 1.00 map units. From the arrangement of both the 3' termini and the coding areas along the viral genome it appears that several RNA species are transcribed from one DNA strand. (Author abstract) (17 Refs)

4. IN VITRO TRANSCRIPTION OF TWO EPSTEIN-BARR VIRUS SPECIFIED SMALL RNA MOLECULES.

Jat P, Arrand JR
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Nucleic Acids Res; 10(11):3407-3425 1982

Cloned DNA from the EcoRI J fragment of EBV has been used as template for in vitro transcription experiments using cell-free extracts prepared from HeLa or KB cells. Two EBV specific RNAs each about 175 bases in length were synthesized and nuclease S1 mapping experiments determined that these in vitro products corresponded precisely to the in vivo species obtained from Raji cells. Thee two RNA molecules are transcribed by RNA polymerase III and in common with other pol III-synthesized RNAs the coding sequences contain intragenic control regions. The relative abundance of the two RNAs synthesized in vitro differs from that observed in vivo. (Author abstract) (48 Refs)

5. TRANSCRIPTS FROM THE CELLULAR HOMOLOGS OF RETROVIRAL ONCOGENES: DISTRIBUTION AMONG CHICKEN TISSUES.

Gonda TJ, Sheiness DK, Bishop JM
Dept. Microbiology and Immunology, Univ. California, San Francisco, CA, 94143
Mol Cell Biol; 2(6):617-624 1982

RNA transcribed from each the four c-onc genes c-myb, c-myc, c-erb, and c-src was quantified in a variety of tissues and cells by dot-blot assay with standardized avian myeloblastosis virus (AMV) 70S virion RNA. Cells examined for levels of c-onc RNAs included fibroblasts, whole embryo, yolk sac, Marek's disease-transformed cells (MSB-1), avian erythroblastosis virus (AEV) erythroblasts and fibroblasts and AMV myeloblasts. Transcription from each c-onc gene was detected (as c-myc, c-erb, and c-src RNA) in nearly all cells and tissues examined, but significant c-myb transcription was detected only in hemopoietic cells. The amount of c-onc RNAs varied, relatively little variation was observed in c-erb levels, a greater range in c-myc and c-src RNA levels was noted, and the greatest variations were exhibited by c-myb levels. Organs expressing the highest levels of c-myb (bone marrow, yolk sac, thymus) are major hemopoietic organs of the chicken, suggesting that c-myb may be expressed in immature hemopoietic cells. The high level of c-myb expression found in AEV-transformed erythroblasts suggests that c-myb function is not restricted to myelomonocytic cells. No obvious correlation existed between susceptibility to transformation and c-onc expression. (40 Refs)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

6. ACUTE LEUKEMIA VIRUSES E26 AND AVIAN MYELOBLASTOSIS VIRUS HAVE RELATED TRANSFORMATION-SPECIFIC RNA SEQUENCES BUT DIFFERENT GENETIC STRUCTURES, GENE PRODUCTS, AND ONCOGENIC PROPERTIES.

Bister K, Nunn M, Moscovici C, Perbal B, Baluda MA, Duesberg PH
Max-Planck-Institut fur Molekulare Genetik, Ihnestrasse 63-73, D-1000 Berlin 33, W. Germany
Proc Natl Acad Sci USA; 79(12):3677-3681 1982

The genetic structure and gene products of E26 virus were analyzed for a comparison with those of AMV. An E26/helper virus complex was found to contain two RNA species: a 5.7-kilobase (kb) RNA than hybridizes with cloned AMV-specific proviral DNA and hence is probably the E26 genome; and an 8.5-kb RNA that is unrelated to AMV and represents helper virus RNA. Thus, E26 RNA is smaller than 7.5-kb AMV RNA. Hybridization of size-selected poly(A)-terminating E26 RNA fragments with AMV-specific DNA indicated that the shared specific sequences are located in the 5' half of the E26 genome as opposed to a 3' location in AMV RNA. In nonproducer cells transformed in vitro by E26, a gag-related nonstructural 135,000-dalton protein (p135) was found. No gag (Pr76) or gag-pol (Pr180) precursors of essential virion proteins, which are present in AMV nonproducer cells, were observed. p135 was also found in cultured E26 virus producing cells of several leukemic chickens, and its intracellular concentration relative to that of the essential virion proteins encoded by the helper virus correlates with the ratio of E26 to helper RNA in virions released by these cells. p135 is phosphorylated but not glycosylated and appears to be coded for by a partial gag gene and by E26-specific RNA sequences, presumably including those shared with AMV. Hence, AMV and E26 appear to use different strategies for the expression of related onc sequences: AMV is thought to encode a transforming protein via a subgenomic mRNA, wherease E26 codes for a gag-related polyprotein via genomic RNA. It is speculated that differences in the oncogenic properties of E26 and AMV are due to differences in their genetic structures and gene products. (32 Refs)

7. POLYSOME-ASSOCIATED PROTEINS IN HERPES SIMPLEX VIRUS-INFECTED CELLS.

Bartkoski MJ
Dellen Lab., Omaha, NE, 68134
J Virol; 43(1):357-360 1982

In the cytoplasm of eucaryotic cells, mRNA is associated with proteins. These mRNA-protein complexes, termed messenger ribonucleoprotein (mRNP) particles, are divided into two functional classes. The first class contains free (non-ribosome-associated) mRNPs which have been termed informosomes by others. The second class of mRNPs, those associated with polysomes, are actively engaged in protein synthesis and are termed polysomal mRNPs. The experiments described in this paper examined the proteins associated with polyribosomes in uninfected and herpes simples virus Type 1-infected cells. The data indicate that after infection with herpes simplex virus Type 1, specific changes occur in the proteins which normally are found associated with these polysomal mRNPs. These changes include both the appearance of new and possibly virus-specific proteins and the loss of normal host-specific proteins. The relationship of these changes to the patterns of protein synthesis in these cells is also discussed. (Author abstract) (36 Refs)

8. EXPRESSION OF HUMAN BETA-INTERFERON CDNA UNDER THE CONTROL OF A THYMIDINE KINASE PROMOTER FROM HERPES SIMPLEX VIRUS.

Reyes GR, Gavis ER, Buchan A, Raj NB, Hayward GS, Pitha PM
Dept. Pharmacology and Experimental Therapeutics, John Hopkins Univ. Sch. Medicine, 725 N. Wolfe St., Baltimore, MD, 21205
Nature; 297(5867):598-601 1982

Transcription of human beta-interferon (IFN-beta) gene and the induction of the gene after replacing the normal 5' flanking sequences with a defined promoter segment from another gene were examined. For this purpose the coding portion of the IFN-beta gene was inserted downstream from the promoter sequence and RNA start site of the thymidine kinase (TK) gene from herpes simplex virus type 1. Expression of interferon activity under the control of the viral TK promoter in this chimeric plasmid was demonstrated by microinjection into nuclei of Xenopus oocytes and by transfection into cells followed by superinfection with herpes simplex virus. (32 Refs)

9. EXPRESSION OF EUKARYOTIC VIRAL AND CELLULAR GENES.

Pettersson RF, Kaariainen L, Soderlund H, Oker-Blom N
Dept. Virology, Univ. Helsinki, Helsinki, Finland
Expression of Eukaryotic Viral and Cellular Genes. London, Academic Press, 324 pp., 1981.

Recent advances in molecular virology, molecular genetics, and recombinant DNA research are combined in a discussion of expression of eukaryotic viral and cellular genes. Structure and expression of DNA virus genes are reviewed with respect to molecular analysis of adenovirus transformation, control of adenovirus messenger (m)RNA production by differential transcription and differential stability of mRNA, an early adenovirus glycoprotein and its association with transplantation antigens, the control of adenovirus early gene expression, and mutational analysis of regulatory elements of simian virus 40. Retrovirus genes are discussed with respect to OK 10 virus-transformed bone-marrow-derived cell line, the transforming insert in the Abelson murine leukemia virus genome, and DNA intermediates in the replication of retroviruses. RNA virus genes are discussed with respect to the genome of single-stranded messenger-sense RNA viruses, influenza virus, capped cellular RNAs, drift and shift of influenza A-type virus, vesicular stomatitis virus and host cell phosphoproteins, initiation of eukaryotic protein synthesis, alphavirus gene products, Semliki Forest virus, RNA containing heterogeneous 5'-terminal nucleotide sequences, and Semliki Forest virus defective interfering RNA using DNA copies. Eukaryotic genes are discussed with respect to structure, organization and developmental expression of chorion multigene families, gene amplification and methotrexate resistance, RNA-protein complexes precipitated by Lupus antibodies, promoter sequences, expression of cloned eukaryotic genes in microorganisms, human genomic DNA-encoding Pro-opiomelanocortin, and functional yeast minichromosomes containing centromeric DNA. (701 Refs)

10. MOLECULAR MECHANISM OF EXTINCTION OF LIVER-SPECIFIC FUNCTIONS IN MOUSE HEPATOMA X RAT FIBROBLAST HYBRIDS: EXTINCTION OF THE ALBUMIN GENE.

Papaconstantinou J, Wong E, Ratrie H, Szpirer C, Szpirer J
Div. Cell Biology, Dept. Human Biological Chemistry and Genetics, Univ. Texas Medical Branch, Galveston, TX, 77550
Somatic Cell Genet; 8(3):363-376 1982

The presence of mouse and rat albumin genes in the mouse x rat hybrid cells is demonstrated, and the extinction of albumin synthesis is shown to be possibly due to the virtual absence of cytoplasmic albumin messenger (m) RNA. The presence and activity of the beta-glucuronidase gene, which is located on mouse chromosome 5, as are the albumin and alpha-fetoprotein (AFP) genes, was established in BJ hybrids (of mouse hepatoma line BWTG3 and rat fibroblast line JF1). Southern blot analyses yielded direct evidence for the presence of the mouse and rat albumin DNA sequences in the hybrids. Reassociation data indicate that there are less than 11 albumin mRNA molecules/cell in the BJ hybrids, but that the parent BWTGE has about 10,900 mRNA molecules/cell; extinction of albumin production is thus related to the greater than 1,000-fold reduction of the mRNA level. That the mechanism of extinction of albumin production acts specifically and most probably involves an inhibition of transcription reinforces the idea that this mechanism is similar to those which in normal development block the expression of fibroblast albumin and AFP genes. (56 Refs)

11. ARRANGEMENT OF LAMBDA LIGHT CHAIN GENES IN MUTANT CLONES OF THE MOPC 315 MOUSE MYELOMA CELLS.

Hozumi N, Wu G, Murialdo H, Baumal R, Mosmann T, Winberry L, Marks A
(c/o Mosmann) Banting and Best Dept. Medical Res., Univ. Toronto, Ontario Cancer Inst., Toronto, Ontario M6G 1L6, Canada
J Immunol; 129(1):260-266 1982

The synthesis of lambda light chains and the arrangement of the lambda-chain genes was examined in cells of the mouse myeloma MOPC 315, which is an alpha lambda2 producer, and in several mutants derived from it. The mutants produce lambda2 chains only (MOPC 315.26, MOPC 315.34, and MOPC 315.37) or fail to produce alpha and lambda2 chains (MOPC 315.35 and MOPC 315.36). Messenger RNA from lambda2 chain-producing cells directed the synthesis of a lambda2 chain precursor and a fragment of the lambda1 chain (lambda1F) in a wheat embryo cell free system, whereas mRNA from the cells that do not produce lambda2 chains directed the synthesis of lambda1F only. DNA from the parental MOPC 315 cells and from the lambda2 chain-producing cells contained discrete EcoRI restriction fragments coding for rearranged lambda1 and lambda2 chain genes and their respective germ-line V and J-C regions. DNA from the non-Ig-producing cells contained fragments coding for the rearranged lambda1 chain gene and the germ-line Vlambda2 region, but it lacked the sequences coding for the rearranged lambda2 chain gene and the germ-line Vlambda1 and J-Clambda1 regions. These results suggest that rearrangements of the lambda1 and lambda2 chain genes occur on different chromosomes in MOPC 315 cells and imply that rearrangements of the lambda1 and lambda2 chain genes on the same chromosome may be mutually exclusive. (Author abstract) (37 Refs)

12. LIFE SPAN OF MRNA IN HUMAN MYELOMA CELLS - A STUDY BASED ON ULTRASTRUCTURAL QUANTITATIVE ANALYSIS OF POLYSOMES.

Yonezawa T, Kitani T, Hiraoka A, Imanaka T
Second Dept. Internal Medicine, Osaka Univ. Medicial Sch., Osaka, Japan
Nippon Ketsueki Gakkai Zasshi; 45(1):103-111 1982

This report is the first study to apply a morphological method in determining the life span of mRNA in human myeloma cells. We quantitated membrane-bound polysomes linked by mRNA, to estimate the life span of mRNA in Ig-producing human myeloma cells. Incubation of the cells with actinomycin D, an inhibitor of mRNA synthesis, resulted in a time-related decrease in the number of polysomes, as evidenced by electron microscopy. In two patients with IgG myeloma, a half life of mRNA was estimated at 4 hr and 3 3/4 hr, respectively. Our findings indicate further that the morphologically discernible ribosome aggregates are identical to the structures designated polysomes in the field of biochemistry. (Author abstract) (16 Refs)

13. TRANSLATION OF MRNA FOR HUMAN GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR.

Lusis AJ, Golde DW, Quon DH, Lasky LA
Div. Hematology/Oncology, Dept. Medicine, UCLA Sch. Medicine, Los Angeles, CA, 90024
Nature; 298(5869):75-77 1982

Translation and partial characterization of a messenger RNA (mRNA) for human granulocyte-macrophage colony stimulating factors (GM-CSF) that stimulates both granulocyte and macrophage colonies are reported. The mRNA was isolated from human T-lymphocyte cell line, and when injected into Xenopus laevis oocytes it directed the synthesis of biologically active GM-CSF. The GM-CSF translated into oocytes also stimulated the growth in agar of a human myeloid leukemia cell line KG-1. As in the case of bone marrow cells, medium from oocytes injected with water or control RNA had no effect on the growth of KG-1 cells. However, homogenates of both injected and uninjected oocytes significantly inhibited cell growth. (21 Refs)

14. INHIBITION OF CELLULAR IMMUNITY IN SMALL CELL BRONCHOGENIC CARCINOMA OF THE LUNG: CHARACTERIZATION OF LOW-MOLECULAR SERUM FACTORS WHICH INHIBIT PROTEIN SYNTHESIS IN NORMAL LYMPHOCYTES (MEETING ABSTRACT).

Manke HG, Drings P, Lenhard V, Dirks HP, Toomes H
Onkologisches Zentrum Heidelberg-Mannheim, Mannheim, W. Germany
Onkologie; 4(5):266 1981

The synthesis of RBC-receptor proteins, a differentiation marker of human peripheral T-lymphocytes, is inhibited in patients with small cell bronchogenic carcinoma. This glycoprotein, which has been briefly characterized by Owen and Fanger as well as by Gurtler persists in the membrane for different periods of time depending on the T-cell population. When protein synthesis, nucleocytoplasmic mRNA transfer and mRNA synthesis are inhibited, normal T-lymphocytes are become depleted of RBC-receptor protein with characteristic temporal kinetics. In small cell bronchogenic carcinoma there is a very profound inhibition of the cellular immune system. In a study of 32 patients with small cell bronchogenic carcinoma the defect in cellular immunity correlated with a decrease in RBC-rosette forming cells and patient lymphocyte proliferation in response to mitogenic stimulation. Serum and serum fractions from patients with low RBC-rosette formation inhibited the expression of RBC-receptor protein by normal human peripheral lymphocytes within 60 min when incubated at 37C. This inhibition coincided with a reduction in protein synthesis (H3-amino acid uptake). The inhibitory serum fraction was further purified by means of high pressure liquid chromatography; the inhibitory trypsin-sensitive fraction lies in the 20,000 dalton region. The present studies refer to an inhibition of protein synthesis possibly on account of induction of a cyclic AMP-dependent protein kinase. (no Refs) (In GER)

15. REVERSIBLE BLOCKING OF MYOGENESIS BY A CHEMICAL CARCINOGEN (MEETING ABSTRACT)

Parker A, Holtzer H
Department of Anatomy, University of Pennsylvania, Philadelphia, PA
Anat Rec; 202(3):8A 1982

EMS (ethyl methanesulfonate), a chemical carcinogen and a mutagen, reversibly blocks the synthesis and assembly of muscle-specific proteins into striated myofibrils; it does not block the synthesis or assembly of the muscle-specific, 10nm, intermediate-sized filaments (MIF). One hundred percent of day 4 myotubes in control cultures displayed normal striated myofibrils. Striated myofibrils were either totally absent or greatly reduced in number in day 4 myotubes that had been treated with EMS for the last 72 hours of culture. The presence of myofibrils was determined by fluorescein-labelled anti-LMM, anti-alpha-actinin, anti-MIF and EM. Myotubes in both day 4 control and day 4 EMS-treated cultures displayed longitudinally-oriented MIF. The multinucleated structures that formed in EMS were atypical in over-all morphology. If the EMS-blocked myotubes were shifted to normal medium for an additional 3 days, they preceeded to assemble large numbers of striated myofibrils, in addition to assembling longitudinally-oriented MIF. Total mRNAs were translated in a rabbit in reticulocytelysate system from cultures that had been treated with EMS for 3 days and from cultures that had been allowed to recover for 3 days. Following separation of the in vitro synthesized labeled proteins in SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis), the fluorograms revealed that the mRNAs from myotubes in EMS for 3 days though translating MIF failed to translate detectable myosin heavy chains. The mRNAs from the recovered myotubes translated both myosin heavy chains and MIF. (no Refs)

16. MOLECULAR AND CELLULAR MECHANISMS IN CARCINOGENESIS (MEETING ABSTRACT)

Rajewsky MF
Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, D- 4300 Essen 1, W. Germany
Molecular and Cellular Mechanisms of Irradiation, March 17-19, 1982, Neuherburg, W. Germany. Gesellschaft fur Strahlen und Umweltforschung MBH 65 pp., 1982.

Structural modifications of DNA in cellular chromatin are primary events in the multistage process of tumorigenesis initiated by chemical carcinogens, ionizing radiation, and UV light. Among the various classes of chemical carcinogens, the alkylating agents have been particularly well characterized with regard to their reaction products in DNA, and sophisticated methodology (including the use of monoclonal antibodies) has been developed for the detection of specific alkylation products. It is not yet clear which molecular processes are preferentially affected, or set into motion, by carcinogen-modified DNA structures, and which alterations of cellular genetic programmes result in the expression of malignant phenotypes. Among the mechanisms to be considered are different types of mutations, altered patterns of DNN methylation or m-RNA processing, gene rearrangements and amplification, and possibly error-prone DNA repair. There is evidence indicating that in order to become malignantly transformed, cells must be proliferating (or have retained the capacity to re-enter the cell cycle; 'Go-cells') at the time of carcinogen exposure. Furthermore, a number of model systems of carcinogenesis indicate a cell type and differentiation stage-dependency of carcinogenic effect. Certain carcinogen-DNA adducts can be specifically recognized, removed and repaired by cellular enzymes which are expressed to varying degrees in different cell types and tissues, individuals, and species. The differential capacity of cells to repair carcinogen-modified DNA (besides intercellular variations in the metabolic conversion of chemicals to their ultimate reactive derivatives), may constitute one of the determinants for the probability of malignant transformation. (no Refs)

17. CELL CYCLE VARIATION IN 125I-LABELED EPIDERMAL GROWTH FACTOR BINDING IN CHEMICALLY TRANSFORMED CELLS.

Robinson RA, Branum EL, Volkenant ME, Moses HL
(c/o Moses) Dept. Cell Biology, Pathology, Mayo Clinic, Foundation and Medical Sch., Rochester, MN, 55905
Cancer Res; 42(7):2633-2638 1982

The chemically transformed AKR-MCA and C3H/MCA-58 cell lines spontaneously arrest growth in the G1 phase of the cell cycle due to nutrient deficiency when grown to saturation density in medium with 10% fetal bovine serum. An examination of 125I-labeled epidermal growth factor (EGF) binding in rapidly growing and G1-arrested cells showed that the G1-arrested chemically transformed cells also have a 10-to 20-fold reduction in the amount of 125I-labeled EGF binding relative to the same cells in the rapidly growing state. Recovery of receptor activity by addition of serum-free medium was inhibited by actinomycin D and cycloheximide, suggesting that new messenger RNA synthesis as well as increased protein synthesis is necessary for the recovery of EGF binding. A comparison of EGF binding in C3H/MCA-58 cells and the transformed parent line in the rapidly growing state showed the same approx level of receptor activity. The rapidly growing AKR-MCA cells had approx one-tenth the amount of EGF binding as did the rapidly growing nontransformed parent line. Analysis of data showed a 10-fold greater number of receptors in the AKR-2B cells relative to the AKR-MCA cells with a lesser difference in receptor affinity. The chemically transformed BP-3T3, like the other two chemically transformed lines, was also demonstrated to arrest growth spontaneously due to nutrient deficiency with an associated 100-fold decrease in EGF binding. Rapidly growing BP-3T3 cells had only slightly less 125I-labeled EGF binding than did the nontransformed parent line in the rapidly growing state. The data indicate that one mechanism for reduction of EGF binding in chemically transformed cells is the propensity of these cells to arrest growth in G1 at saturation density due to low-mol-wt nutrient deficiency, a state associated with decreased EGF binding. (25 Refs)

STRUCTURE AND LEVELS OF RIBOSOMAL RNA

18. VARIATIONS IN THE ACTIVITY OF NUCLEOLAR ORGANIZERS IN DIFFERENT TISSUES, DEMONSTRATED BY SILVER STAINING OF HUMAN NORMAL AND LEUKEMIC CELLS.

Reeves BR, Casey G, Harris H
Dept. Cytogenetics and Immunogenetics, Inst. Cancer Res., Royal
Marsden Hosp., Fulham Road, London SW3 6JJ, England
Cancer Genet Cytogenet; 6(3):223-230 1982

A simple silver-staining technique that demonstrates those nucleolar organizing regions of metaphase chromosomes which are transcriptionally active during the preceding interphase (AgNORs) has been applied to cells obtained from the bone marrow and mitogen-stimulated peripheral blood lymphocyte cultures of hematologically normal individuals and patients with various forms of leukemia. In the majority of bone marrow cells from the normal controls and many of the patients, the numbers of cells with detectable AgNORs, and the staining intensities in those cells which were AG+, were markedly reduced compared with the levels found in blood lymphocytes. The numbers of cells having satellite associations and the numbers of chromosomes participating in these associations also generally reflected the proportions of AgNORs present. When patterns of bone marrow silver staining were compared between patients with leukemia, distinct differences were found which could be correlated with cytology. It is suggested that different cell types have characteristic AgNOR staining profiles, reflecting specific regulation of ribosomal RNA synthesis in particular cell lineages. AgNOR staining may indicate, therefore, the predominant cell types that divide in the bone marrows of patients with different forms of leukemia. (Author abstract) (23 Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

19. LABELED 1,N(6)-ETHENOADENOSINE AND 3,N(4)-ETHENOCYTIDINE IN HEPATIC RNA OF MICE GIVEN [ETHYL-1,2-3H OR ETHYL-1-14C] ETHYL CARBAMATE (URETHAN).

Ribovich ML, Miller JA, Miller EC, Timmins LG
(c/o Miller) McArdle Lab. Cancer Res., Univ. Wisconsin Center
Health Sciences, 450 North Randall Ave., Madison, WI, 53706
Carcinogenesis; 3(5):539-546 1982

Injection of a single dose of [ethyl-1,2-3H] or [ethyl-1-14C]ethyl carbamate into 12-day old male [C57BL/6 x C3H/He]F1 mice or of [ethyl-1,2-3H]ethyl carbamate into adult male A/Jax mice resulted in the formation of labeled 1,N6-ethenoadenosine and 3,N4-ethenocytidine adducts in the hepatic RNA. These adducts were characterized by comigration on hplc of 3H or 14C in enzymatic hydrolysates of the RNA with synthetic standards. Both the ethenoadenosine and ethenocytidine were further characterized by their conversion to acetylated products that comigrated with acetylated synthetic standards. The ethenoadenosine was also converted by anhydrous trifluoroacetic acid to a product that comigrated with synthetic 1,N6-ethenoadenine. The levels of adducts in the hepatic RNA 12 hr after a single injection of 0.5-0.6 mg of ethyl carbamate/g body wt were 6-10 and 2-3 pmol/mg RNA of ethenoadenosine or ethenocytidine, respectively. No labeled ethenoadenosine or ethenocytidine could be detected in the hepatic RNA of mice given [1-14C]ethanol, an enzymatic hydrolysis product of ethyl carbamate. These data indicate that ethyl carbamate may be metabolically activated by dehydrogenation to vinyl carbamate and subsequent epoxidation of the latter compound as previously proposed. Vinyl carbamate epoxide may form etheno derivatives in a manner analogous to that demonstrated for chloroethylene oxide, an electrophilic metabolite of vinyl chloride. Vinyl carbamate has been shown to have the same spectrum of tumor induction as ethyl carbamate but to be much more active than the latter carcinogen. (Author abstract) (37 Refs)

20. HIGH SALT EFFECT ON RNA SYNTHESIS IN KREBS ASCITES TUMOR CELLS.

Gokce S, Kan B, Kirdar B, Bermek E
Biyofizik Kursusu, Istanbul Tip Fakultesi, Capa, Istanbul, Turkey
Experientia; 38(6):666-667 1982

The incubation of Krebs ascites tumor cells in medium with a high salt concentration resulted in a partial inhibition of nuclear RNA synthesis. The residual RNA polymerase activity in such nuclei was only slightly inhibited by low concentrations (50 nM) of alpha-amanitin. This finding suggested an inhibition of RNA polymerase II activity under conditions of medium hypertonicity. Indeed, RNA polymerase II, isolated from the nuclei of cells exposed to hypertonicity, revealed only half of the control activity. On the other hand, RNA polymerase I was not affected by hypertonicity. Moreover, chromatin fractions isolated from cells incubated in hypertonic or isotonic medium were equally template-active in RNA synthesis. (Author abstract) (26 Refs)

21. ANTITUMOR EFFECT OF RNASES MODIFIED BY COVALENT BINDING WITH DEXTRAN M-AMINOBENZYLHYDROXYLMETHYL ETHER.

Kurinenko BM, Kladova MS, Penzikova GA, Oreshina MG, Bulgakova RSh
Dept. Microbiology, State Univ., Kazan, USSR
Antibiotiki; 27(5):336-341 1982

Antitumor activities of native RNAse and RNAse modified by covalent binding with dextran m-aminobenzylhydroxylmethyl ether (DMAE) were compared in random-bred albino rats inoculated with 7-day Ehrlich ascites carcinoma (EAC) or sarcoma 37. On day 2 after tumor transplantation, the mice received ip injection of pancreatic RNAse or of RNAse isolated from Actinomyces rimosus. Native pancreatic RNAse had no antitumor activity (inhibitions of growths of EAC and sarcoma 37 were 2.2% and 10.5%, respectively). The native RNAse from A rimosus provided a 15.3% inhibition of growth of EAC and a 25.7% inhibition of growth of sarcoma 37. Covalent binding with DMAE increased the antitumor activity of both pancreatic RNAse (14.4-29.2% inhibition of EAC and 27.3-40.7% inhibition of sarcoma 37) and RNAse from A rimosus (25.2-50.7% and 40.1-55.5% inhibition, respectively). The increased antitumor activities of the modified derivatives were correlated with their increased half-lives in the ascitic fluid (AF). The differences in biological activities of pancreatic RNAse and RNAse from A rimosus were associated with greater sensitivity of the pancreatic enzyme to AF inhibitors. (13 Refs) (In RUS)

22. INCREASED AMOUNTS OF DOUBLE-STRANDED RNA IN THE CYTOPLASM OF RAT LIVER FOLLOWING TREATMENT WITH CARCINOGENS.

Clawson GA, Smuckler EA
(c/o Smuckler) Dept. Pathology, HSW547, Univ. California, San Francisco, CA, 94143
Cancer Res; 42(8):3228-3231 1982

Cytoplasmic RNA was isolated from control rats or at 48 hr following carcinogen administration. A significant quantity (0.6%) of double-stranded RNA was present in control preparations, as assessed by digestion with RNase III. Following carcinogen treatment of rats, this percentage increased significantly. The results suggest that the altered transport of repetitive sequences which is induced by carcinogen treatment involves alterations in the metabolism of double-stranded RNA sequences. (Author abstract) (60 Refs)

OTHER RELATED STUDIES

23. HERPESVIRUS-SPECIFIC RNA AND PROTEIN IN CARCINOMA OF THE UTERINE CERVIX.

McDougall JK, Crum CP, Fenoglio CM, Goldstein LC, Galloway DA
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Proc Natl Acad Sci USA; 79(12):3853-3857 1982

Cloned probes of herpes simplex virus type 2 DNA were used in cytological hybridization experiments to detect herpesvirus RNA transcripts in the neoplastic cells of tumors of the uterine cervix. Virus-specific RNA was shown to represent transcription of limited regions of the genome, of which one is known to code for a DNA-binding protein that can be found by immunoperoxidase staining in the neoplastic cells of these tumors and has also been detected in cells transformed in vitro by this virus. (Author abstract) (56 Refs)

24. EPSTEIN-BARR VIRUS RNA VIII. VIRAL RNA IN PERMISSIVELY INFECTED B95-8 CELLS.

Hummel M, Kieff E
(c/o Kieff) Dept. Biology, Medicine, Section Infectious Diseases, Kovler Viral Oncology Lab., Univ. Chicago, Chicago, IL, 60637
J Virol; 43(1):262-272 1982

More than 50 RNAs expressed by Epstein-Barr virus late in productive infection have been identified. B95-8 infected cells were induced to a relatively high level of permissive infection with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate. Polyadenylated RNAs were extracted from the cell cytoplasm, separated by size on formaldehyde gels, transferred to nitrocellulose, and hybridized to labeled recombinant Epstein-Barr virus DNA fragments. Comparison of RNAs from induced cultures with RNAs from induced cultures also treated with phosphonoacetic acid to inhibit viral DNA synthesis identifies two RNA classes: a persistent early class of RNAs whose abundance is relatively resistant to viral DNA synthesis inhibition and a late class of RNAs whose abundance is relatively sensitive to viral DNA synthesis inhibition. The persistent early and late RNAs are not clustered but are intermixed and scattered through most of segments UL and US. The cytoplasmic polyadenylated RNAs expressed during latent infection were not detected in productively infected cells, indicating that different classes of viral RNA are associated with latent and productive infection. Non-polyadenylated small RNAs originally identified in cells latently infected with Epstein-Barr virus are expressed in greater abundance in productively infected cells and are part of the early RNA class. (Author abstract) (53 Refs)

25. ATTENUATION IN THE CONTROL OF SV40 GENE EXPRESSION.

Hay N, Skolnik-David H, Aloni Y
Dept. Genetics, Weizmann Inst. Science, Rehovot 76100, Israel
Cell; 29(1):183-193 1982

Nuclei and viral transcriptional complexes were prepared from cells infected with simian virus 40 and incubated in vitro in the presence of alpha-32P-UTP. The in vitro elongated viral RNA appeared with a peak of 5S in sucrose gradients and hybridized preferentially to a promoter-proximal region of SV40 DNA. Treatment of infected cells with proflavine led to transcription of elongated RNA, while treatment of cells with 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole, a drug known to enhance premature termination, augmented accumulation of the promoter-proximal RNA. The in vitro elongated RNA produced a major band of 93-95 nucleotides in length in acrylamide gel. This RNA was found to map between the major initiation site at nucleotide 243 and nucleotides 335-337. The significance of these observations with respect to the transcription termination signal and the control of SV40 gene expression is discussed. (Author abstract) (62 Refs)

26. CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE-DEPENDENT PROTEIN PHOSPHORYLATION AND THE CONTROL OF LEUKEMIA L1210 CELL GROWTH.

Mednieks MI, Jungmann RA, DeWys WD
Lab. Biological Structure, Natl. Inst. Dental Res., Building 30, Room 211, Bethesda, MD, 20205
Cancer Res; 42(7):2742-2747 1982

Synergistic increases in the survival of mice bearing an L1210 leukemia tumor have been demonstrated previously after treatment with 1,3-bis(2-chloroethyl)-1-nitrosourea together with theophylline over those treated with either agent alone. These results imply that manipulation of cyclic adenosine 3':5'-monophosphate (cyclic AMP) levels in L1210 cells may result in alteration of sensitivity to chemotherapy and alterations in tumor growth. In the present study, we have shown that in vivo treatment of L1210 cells with theophylline results in changes in intracellular cyclic AMP-dependent protein kinase activity levels as well as in an apparent redistribution of both the nuclear and cytoplasmic isozymes. Biochemical events in the tumor cells immediately after administration of theophylline in vivo or a cyclic AMP analog (8-parachlorophenylthio cyclic adenosine 3':5'-monophosphate) in vitro were independent of the presence of 1,3-bis(2-chloroethyl)-1-nitrosourea. The changes apparently involve signal transduction via the adenylate cyclase system and manifest as: (a) increased sensitivity of cyclic AMP-dependent protein kinase to activation by cyclic AMP after treatment of L1210 cells with theophylline; (b) decrease in endogenous nuclear protein phosphorylation sites; and (c) protein kinase isozyme redistribution between nuclear and extranuclear compartments, ie, a relative increase of the Type I isozyme activity in the nuclear and of the Type II isozyme activity in the 900 x g supernatant fractions after treatment of the mice of theophylline. The relative activity increases are accompanied by relative decrease of Type II activity from the nucleus and Type I isozyme activity from the 900 x g extranuclear supernatant fraction. These events appear temporally related to changes in nuclear RNA metabolism as evidenced by altered kinetics of RNA precursor uptake and incorporation into tumor cell RNA after treatment. These results imply that the cyclic AMP-dependent phosphorylative modification of intracellular proteins may play a regulatory role in tumor cell growth and in theophylline-mediated tumor regression. (Author abstract) (42 Refs)

27. SYNTHESIS OF PREMATURELY TERMINATED LATE TRANSCRIPTS OF POLYOMA VIRUS DNA IS RESISTANT TO INHIBITION BY 5,6-DICHLORO-1-BETA-D-RIBOFURANOSYLBENZIMIDAZOLE.

Montandon PE, Acheson NH
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
J Gen Virol; 59(part2):367-376 1982

Exposure of mouse kidney cells to 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole (DRB) (75 to 300 uM) during the late phase of infection by polyoma virus resulted in nearly complete (90 to 98%) inhibition of virus RNA synthesis. Sedimentation analysis revealed that, although the synthesis of high mol wt (greater than 10S) virus RNA was inhibited in a manner parallel to that of total virus RNA, the synthesis of small (3S to 7S) virus RNA was inhibited by only 40 to 50% in the presence of DRB. As a result, virus RNA synthesized in the presence of DRB contained a peak at 3S to 7S in addition to residual high mol wt virus RNA. Small virus RNA from either untreated or DRB-treated cells contained three- to six-fold higher levels of transcripts from the DNA fragment which lies between the BamHI and BglI sites (58.0 to 72.2 map units) than from DNA fragments covering the rest of the virus genome. Furthermore, 80% of the small RNA which hybridized to this fragment was complementary to the L strand of virus DNA. These results suggest that L strand transcripts are initiated within the BglI-BamHI DNA fragment and that a portion of these transcripts is prematurely terminated within several hundred nucleotides of the site(s) of initiation. DRB had little effect on the synthesis of these prematurely terminated RNAs. (Author abstract) (33 Refs)

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RNA TRANSCRIPTION/ SYNTHESIS

1. SELECTIVE INHIBITION OF ADENOVIRUS TYPE 2 EARLY REGION II AND III TRANSCRIPTION BY AN ANISOMYCIN BLOCK OF PROTEIN SYNTHESIS.

Shaw AR, Ziff EB
Rockfeller Univ., New York, NY, 10021
Mol Cell Biol; 2(7):789-799 1982

Transcriptional regulation of adenovirus Type 2 (Ad-2) early gene expression was studied. The early period was dissected into a series of stages by blocking protein synthesis with the antibiotic anisomycin. Selective blockage of EII and EIII was used to assess the role of chromatin structure change in the activities on EII and EIII. Anisomycin (100 uM) was added to one portion of an exponentially growing HeLa cell culture, and 30 min later the culture and drug-free control were concentrated for virus infection. In the control culture, EIa, EII, EIII, and EIV were transcriptionally active, and nuclear RNA from each of the regions accumulated. In the drug-treated culture, EIa and EIV were also active, and RNA accumulation was comparable to that of the control. Accumulation of messenger RNA (mRNA) from regions EIa and EIV proceeded at

HE 20.3172/2.

essentially the same rate in the presence or absence of the drug. Anisomycin treatment caused a dramatic decrease, estimated to be greater than 10-fold, in the steady-state level of EII and EIII mRNA. The EII-EIII transcription rate was greatly repressed in the presence of anisomycin. Resultes confirmed that the principal effect of anisomycin is at the level of transcription and is confined to regions EII and EIII. Similarity in the banding patterns suggested that a protein synthesis block which decreases transcription from the EII and EIII promoters by greater than 90% does not cause a difference in the pattern of deoxyribonuclease I sensitivity of the repressed chromatin relative to the transcriptionally active chromatin in control cells. (26 Refs)

2. EFFECT OF ANTHRACYCLINE ANALOGUES ON THE APPEARANCE OF NEWLY SYNTHESIZED TOTAL RNA AND MESSENGER RNA IN THE CYTOPLASM OF ERYTHROLEUKEMIA CELLS.

Long BH, Willis CE, Prestayko AW, Crooke ST
Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
Mol Pharmacol; 22(1):152-157 1982

Effects of the structural analogs adriamycin (ADM), daunomycin (DNM), carminomycin (CMM), 4-demethoxydaunomycin (4D-DNM), pyrromycin (PYM), marcellomycin (MCM), and aclacinomycin (ACM) upon total RNA synthesis and appearance of total RNA and polyadenylated (poly(A)+)-RNA in the cytoplasm of uninduced Friend erythroleukemia cells were studied. Each drug was tested at six different concentrations and compared with the av of two controls in three separate experiments. Generally, there were greater differences between the effects of different drugs than were exhibited by the same drug upon the different RNA populations. The differences were clearer when expressed as median dose (IC50) values. The Class II anthracyclines, MCM and ACM, inhibited RNA synthesis by 50% at 60 nanoM, which is 20-50 fold lower than the IC50 value for class I anthracyclines, DNM and ADM. Inhibition of the appearance of poly(A)+-RNA in the cytoplasm closely paralleled inhibition of total RNA synthesis for ADM, DNM, and CMM, whereas the appearance of poly(A)+-RNA was less sensitive to inhibition by the Class II drugs. IC50 values for inhibition of the appearance of total RNA into the cytoplasm were consistently 1/2 to 1/3 the respective IC50 values for total cellular RNA synthesis inhibition, suggesting that one possible factor in the effects of these anthracyclines is alteration of post-transcriptional events. Pre-messenger RNA and pre-ribosomal RNA effects probably play a minor role in inhibiting the appearance of RNA in the cytoplasm compared to the activity at the transcriptional level. (30 Refs)

3. 9-DEAZAADENOSINE, A NEW POTENT ANTITUMOR AGENT (MEETING ABSTRACT).

Chu MY, Landry LB, Klein RS, Lim MI, Bogden AE, Crabtree GW
Division of Biology, Roger Williams General Hospital, Brown University, Providence, RI, 02908
Proc Am Assoc Cancer Res; 23:867 1982

The growth inhibition of 9-deazaadenosine (9-DAA), against 9 human solid human tumor lines (HRT-18; mesothelioma, VAMT-1; EP Breast; HCT-8, melanoma, Tang; MW Breast; pancreatic carcinoma, DAN; lung carcinoma LX-1 and ovarian carcinoma) was evaluated. ID50 values ranged from 1-8.5 x 10-8M. Studies with pancreatic carcinoma, DAN, in ATS-mice showed that 9-DAA (0.5 mg/kg/day for 3 days) reduced tumor weight to 16% of controls. Some weight losses and/or deaths were noted. Host toxicity was reduced when p-nitrobenzyl-6-thioinosine (NBMPR) a nucleoside transport inhibitor, was used in combination with 9-DAA. In vitro studies with pancreatic carcinoma, DAN and ovarian carcinoma cells showed that 9-DAA (10-5M for 2 hr) caused 34 and 68% inhibition of [3H]-uridine incorporation into RNA and DNA, respectively, and inhibited [3H]-thymidine incorporation into DNA by 80%. In these studies, peak which appeared in the triphosphate region of nucleotide profiles (determined by anion-exchange high pressure liquid chromatography) was tentatively identified as 9-deazaATP. These studies demonstrate that (1) 9-DAA is a potent growth inhibitor of 9 types of human solid tumor cell lines in vitro and of pancreatic carcinoma, DAN in vivo, (2) host toxicity to 9-DAA can be reduced by pretreatment with NBMPR, (3) 9-DAA can be incorporated into the nucleotide pools of treated cells and (4) 9-DAA may exert its effects, in part, by inhibiting the synthesis of RNA and DNA. (no Refs)

4. RESPONSES OF HUMAN CHONDROSARCOMAS TO N6-MONOBUTYRYL CYCLIC AMP, PROSTAGLANDIN A1 AND SERUM FACTORS (MEETING ABSTRACT).

McCumbee WD, Lebovitz HE
Duke Medical Center, Durham, NC, 27710
Fed Proc; 41(3):736 1982

In cartilage, RNA synthesis is stimulated by serum from intact (Norm) and growth hormone-treated hypophysectomized (GH-Rx) rats but not by serum from untreated hypophysectomized (Hypx) rats. N6-monobutyryl cyclic AMP (MBcAMP) either stimulates (embryonic chick cartilage) or has no effect (rat costal cartilage) on RNA synthesis, whereas prostaglandin A1 (PGA1) profoundly inhibits the synthesis of RNA. The present study investigated the in vitro regulation of [3H]uridine incorporation into RNA of 5 human chondrosarcomas to determine if malignant human chondrocytes are under similar metabolic and hormonal regulation. Uridine incorporation into RNA was stimulated by growth hormone-dependent serum factors in one tumor and by growth hormone-independent factors in 2 tumors. Two tumors were unresponsive to serum stimulation. PGA1 markedly inhibited uridine incorporation into RNA in all 5 tumors (56 to 80%). MBcAMP inhibited uridine incorporation in 4 of the 5 tumors by 32 to 50%. The data indicate that chondrosarcoma cells. This is similar to its effect on normal chondrocytes. MBcAMP regulation differs from that observed in normal chondrocytes: MBcAMP inhibited RNA synthesis in most of the chondrosarcomas studied. Tumor responses to serum factors vary among individual tumors with one responding similarly to normal cartilage and the others not. (no Refs)

5. BONE MARROW (BM) TOXICITY SECONDARY TO FLUOROPYRIMIDINE (FP) DRUGS: INCORPORATION INTO RNA AS THE MAJOR DETERMINANT OF BM TOXICITY (MEETING ABSTRACT).

Diasio RB, Schuetz JD, Banks W, Wallace H
Medical College of Virginia, Richmond, VA, 23298
Proc Am Assoc Cancer Res; 23:843 1982

FP toxicity in host and tumor cells has been attributed to either; 1) inhibition of thymidylate synthetase activity (TSA) by fluorodeoxyuridylate (FdUMP) or 2) RNA dysfunction secondary to incorporation of FP into RNA. The relative contribution of either mechanism to the toxicity of fluorouracil (FU), fluorouridine (FUrd), fluorodeoxyuridine (FdUrd), and 5'deoxyfluorouridine (5'dFUrd) is unclear. The present study correlates inhibition of TSA and FP incorporation into RNA with

BM toxicity. BM cells from CF1 mice were incubated for 60 min to a dose range of each FP after which the cells were cloned in vitro to determine equitoxic doses producing 50% (IC50) and 75% (IC75) inhibition of colony formation. At the IC50 of FU (10.4uM) FUrd (0.18uM), FdUrd (6.5uM), and 5'dFUrd (168uM) parallel studies examined: 1) inhibition of TSA by tritium release assay, and 2) incorporation of radiolabelled FP into RNA. In triplicate studies: 1) FdUrd resulted in rapid + complete inhibition of TSA while FU, FUrd, and 5'dFUrd had no TSA inhibition by 60 min, and 2) incorporation of FP into RNA was similar throughout the 60 min incubation with a 60 min level for FU (3.5pMol/ugRNA), FUrd (4.4pMol/ugRNA), FdUrd (1.1pMol/ugRNA), and 5'dFUrd (3.1pMol/ugRNA). Increasing the dose to an IC75 of FU (19uM), FUrd (0.33uM), FdUrd (45uM), and 5'dFUrd (286uM) resulted in essentially no change in the pattern of TSA inhibition while there was marked increase in the incorporation of FP into RNA throughout the 60 min for all four FP's. (no Refs)

6. THE GLUCOCORTICOID HORMONE REGULATED MURINE MAMMARY TUMOR VIRUS TRANSCRIPTION UNIT.

Ucker DS
University of California, San Francisco, CA
Diss Abstr Int [B]; 42(10):3925-B 1982

The glucocorticoid receptor protein, complexed with an active ligand such as dexamethasone, selectively stimulates the transcription of murine mammary tumor virus (MTV) sequences integrated into the genome of cultured rat hepatoma (HTC) cells. Analyses of transcriptional rates of proviral and flanking cellular sequences, and in corresponding 'preinsertion fragments' have revealed that the region of the cellular genome into which an MTV provirus integrates need not itself be either transcriptionally active or hormonally responsive. Thus hormonal regulation of viral transcription appears to reflect the presence of regulatory sequences within the MTV DNA itself. Using a line of infected HTC cells that produces a detectable basal level of MTV RNA, we have compared the structure of MTV transcripts synthesized in hormone treated and untreated cells. Two species of MTC transcripts (7.8kb and 3.8kb) are produced in the absence of dexamethasone, and both species are proportionally induced in its presence; moreover, the 5' termini and polyA addition sites of these transcripts are identical and are not altered by hormonal induction. The 5' terminus of nascent MTV RNA is indistinguishable from that of mature viral mRNA, is independent of the proviral integration site, and maps to the sequence at the 5' terminus of virion RNA residing in the MTV long terminal repeat (LTR). The concentration of 5' MTV termini in nascent transcripts increased rapidly upon dexamethasone treatment. The concentration of 3' termini increases in similar fashion, albeit lagging seven minutes behind 5' termini induction. This lag reflects the transit time for RNA polymerase II across the MTV transcription unit. In vitro labelling of the nascent chains by runoff transcription indicates that the specific increase in the rate of MTV RNA synthesis is half maximal within nine minutes of hormone addition. Therefore, basal synthesis of MTV RNA in these cells appears to be initiated at a single site within the MTV LTR, and dexamethasone rapidly stimulates expression from that same site. (no Refs)

7. BIOLOGICAL EFFECTS OF RADIATION WITH HEAVY IONS.

Kiefer J
Strahlenzentrum der Universitat, D-6300 Giessen, W. Germany
Naturwissenschaften; 69(6):260-265 1982

Experiments with accelerated heavy ions may contribute to the understanding of biological radiation action. After outlining the theoretical background experiments are described which were carried out at the UNILAC-machine (Gesellschaft fur Schwerionenforschung, Darmstadt, Germany) where ions up to uranium can be accelerated to maximal specific energies of 10 MeV/u. Yeast cells served as biological test systems with the synthesis of ribosomal RNA (r-RNA), colony-forming ability and mutation induction as experimental endpoints. A relationship between action and energy deposition by individual particles can be demonstrated for the inhibition of r-RNA synthesis, in other cases the ion energy plays also an important role indicating that the interaction of delta-electrons from different particles contributes significantly to the biological effect. (Author abstract) (13 Refs) (In GER)

STRUCTURE, ACTIVITY AND LEVELS OF MESSENGER RNA

8. ALTERNATIVE RNA PROCESSING IN CALCITONIN GENE EXPRESSION GENERATES MRNAS ENCODING DIFFERENT POLYPEPTIDE PRODUCTS.

Amara SG, Jonas V, Rosenfeld MG, Ong ES, Evans RM
Div. Endocrinology, Sch. Medicine, Univ. California, San Diego, La Jolla, CA, 92093
Nature; 298(5871):240-244 1982

Alternative processing of RNA transcripts from the calcitonin gene results in the production of distinct mRNAs encoding the hormone calcitonin or a predicted product referred to as calcitonin gene-related peptide (CGRP). The calcitonin mRNA predominates in the thyroid while the CGRP-specific mRNA appears to predominate in the hypothalamus. These observations lead us to propose a model in which developmental regulation of RNA processing is used to increase the diversity of neuroendocrine gene expression. (Author abstract) (34 Refs)

9. CONSTRUCTION OF A CDNA LIBRARY FOR THE STUDY OF RAT HEPATOMA MRNA'S.

Branwood AM
Columbia University, New York, NY
Diss Abstr Int [B]; 42(9):3638-B 1982

A cDNA library was constructed for a 'butter yellow' (dimethylaminoazobenzene) induced rat hepatoma cell line (HTC) by inserting double-stranded cDNA molecules into the plasmid vector pAT153, with the aid of blunt-end ligation. Double-stranded cDNA was prepared from HTC polysomal poly (A+) mRNA, and a random population of cDNAs corresponding to the original poly (A+) mRNAs was thus obtained. A derivative of pBR322, pAT153, was chosen for its number of unique endonuclease restriction sites located within antibiotic resistance genes and its safety in handling. Transformation conditions were optimized such that, when the Escherichia coli strain HB101 was transformed by the recombinant plasmids, the efficiency was high enough to ensure that the cDNA library was representative of most of the original RNA population (3.8x10(3) colony-forming units per ug plasmid DNA). The bacterial colonies containing the recombinant molecules were screened initially by response to antibiotics, and subsequently by Grunstein-Hogness hybridization. Ampicillin-resistant, tetracycline-sensitive colonies showing a positive Grunstein-Hogness response were picked, and the plasmids were isolated and tested by the Dot hybridization technique with labeled rat liver cDNA and HTC cDNA probes. One HTC poly (A+) mRNA sequence represented by a recombinant plasmid was at a higher concentration in rat liver poly (A+) mRNA than nonrecombinant HTC poly (A+) mRNA, and from Northern blot data found to be at its highest concentration in rat liver nuclei. Some plasmids were further characteristized by sizing on an agarose (1.5%) gel. (no Refs)

10. DIBUTYRYL CYCLIC AMP TREATMENT MIMICS OVARIECTOMY: NEW GENOMIC REGULATION IN MAMMARY TUMOR REGRESSION.

Huang FL, Cho-Chung YS
Cellular Biochemistry Section, Lab. Pathophysiology, NCI, Bethesda, MD
Biochem Biophys Res Commun; 107(1):411-415 1982

The possibility that the regression process of hormone-dependent tumors is regulated by a transcriptional event and that the regressions produced by hormone removal and dibutyryl cyclic (dc)AMP treatment are evoked by similar or identical mechanisms was investigated. The study presents the first evidence of differential gene expression during growth and regression of hormone-dependent dimethylbenz(a)anthracene-induced rat mammary carcinoma. Changes in translation products demonstrable during regression appeared to be specifically related to the hormone-independence of the tumors. As early as 6 hr post ovariectomy or dcAMP treatment (10 mg/200 g rat/day, sc), when there was no appreciable change in tumor size, the in vitro synthesis of several polypeptides instructed by poly(A)RNAs of tumors was either depressed or stimulated, indicating that these changes in gene expression are an early event in tumor regression. Both dcAMP and ovariectomy induced the same changes in the translation products. Thus estrogen and cyclic AMP may counteract each other at the nuclear level in the growth control of hormone-dependent mammary tumors. (17 Refs)

11. MURINE B LYMPHOMAS: MODELS FOR IMMUNOGLOBIN EXPRESSION IN B CELL DEVELOPMENT.

Word CJ
University of Virginia, Charlottesville, VA
Diss Abstr Int [B]; 42(9):3582-B 1982

Individual clones of three B lymphoma cell lines (A20-1.11, X16C-4.3, K46-056) were found to synthesize two intracellular species of gamma 2a heavy chain which differ in apparent size by approx 6,000 daltons. The smaller gamma 2a heavy chain species is secreted by the cell and the larger gamma 2a heavy chain species is localized on the external cell membrane. Two species of mRNA, which apparently encode the two gamma 2a heavy chain species, were detected in the cytoplasm of the cells. It appears that the smaller (2.0 kb) mRNA species codes for the secreted gamma 2a heavy chain and the larger mRNA species (4.0 kb) codes for the membrane gamma 2a heavy chain. Fusion of the A20-1.11 or X16C-4.3 B lymphoma to myeloma cell lines results in hybrids expressing the more differentiated myeloma phenotype. That is, the expression of the secreted form of the lymphoma gamma 2a heavy chain is amplified as much as 150 fold while the expression of the membrane form of the lymphoma gamma 2a heavy chain polypeptide and corresponding mRNA is greatly diminished or abolished in the hybrid. Less than five percent of normal B lymphoid cells or plasma cell tumors express lambda light chains, and only rare tumors have been described that simultaneously express both lambda and kappa light chains in a single cell. However, three cloned B lymphoma cell lines (K46-056, B17-1.11, X16C-4.3) were found to express both lambda and kappa light chains. Different patterns of assembly of the light chains to the heavy chains were found. (no Refs)

12. ASYNCHRONOUS EXPRESSION OF IMMUNOGLOBULIN GENES IN A HUMAN B CELL LYMPHOMA (MEETING ABSTRACT).

Fan K, Hough AJ
Department of Pathology, Veterans Administration Medical Center, Little Rock, AR
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

A cell line was established from a well-differentiated human B cell lymphoma. The cloned and suspension-cultured cells synthesized and secreted large amounts (6 per cent of the cytoplasmic protein) of K-light chain without evidence of heavy chain secretion. By immunofluorescence reaction, almost all of the cells showed strongly detectable introcytoplasmic and cell surface K-light chain (cIg+, sIg+), whereas only 5 per cent of the cells showed weakly detectable cytoplasmic mu-heavy chain. After exposure to mitogens, the mu-chain became detectable cytoplasmically in 80 per cent of the cells, whereas the K-chain expression remained unchanged. Furthermore, in a wheat germ cell-free protein synthesis system, the mRNAs isolated from microsomes of the mitogen-unexposed lymphoma cells were able to direct equimolar synthesis of both K- and micro-chain. These findings suggest that expression of light and heavy chain immunoglobulin genes in human B cell may be under separate regulatory mechanisms and that colored B cells can synthesize immunoglobulin subunits asynchronously. In this cell line, it also appears that translational control may play a role in heavy chain gene expression, which is also modifiable by exposure to B cell mitogens such as dextran sulfate or bacterial lipopolysaccharide. (no Refs)

13. ALTERED LEUKOCYTE ALKALINE PHOSPHATASE (LAP) GENE EXPRESSION IN CHRONIC GRANULOCYTIC LEUKEMIA (CGL) BLAST CELLS (MEETING ABSTRACT).

Miller DM, Yang A
Simpson Memorial Research Institute, University of Michigan, Ann Arbor, MI, 48109
Proc Am Assoc Cancer Res; 23:69 1982

We have studied the mechanism of LAP elevation in CGL blast phase cells. LAP demonstrates electrophoretic heterogeneity with two bands of enzyme activity in polyacrylamide-Triton gels; LAPs and LAPf. Twelve of fourteen normal subjects demonstrated only LAPs in an extract of their granulocytes, while two had very slight amounts of LAPf. Six patients with stable phase CGL also had only LAPs present in their granulocytes. However, thirteen of fourteen patients who clinically had blast phase CGL demonstrated the presence of both LAPs and LAPf. Complementary DNA (cDNA) was synthesized from poly-A RNA isolated from the cells of this patient by phenol extraction and oligo-dT cellulose chromatography. Hybridization of this cDNA to its template RNA (blast phase cells) and to RNA isolated from stable phase CGL cells was performed. The initial velocity of hybridization was 50% less for the stable phase RNA than for the blast phase RNA. The degree of hybridization at large RNA excess was also 50% less with the stable phase RNA than with the template RNA. These data indicate that approximately 50% of the messenger RNA(mRNA) sequences of the blast phase CGL cells are not represented in the stable phase cells signifying major transcriptional alterations in these cells. It is likely that LAPf makes up a considerable proportion of the mRNA synthesized by CGL blast cells expressing this enzyme. Thus the expression of this 'tumor marker' gene must be under transcriptional control. (no Refs)

14. POLYSOMAL DISTRIBUTION OF MRNA IN THE CELL CYCLE OF MOUSE S-180 ASCITES CELLS (MEETING ABSTRACT).

Goeghegan TE, Knoop SJ
University of Louisville, Louisville, KY, 40292
Fed Proc; 41(3):1285 1982

Mouse sarcoma-180 ascites cells contain a limited population of cytoplasmic messenger ribonucleoprotein (mRNP) whose translation appears to be restricted in vivo as well as in vitro. To determine if this population of mRNP changes during the cell cycle stages by centrifugation through ficoll gradients. The distribution of cells able to incorporate (3H)-thymidine into DNA suggests that fractionation of ascites cells on the basis of size will yield cell cycle enriched populations. A bi-modal distribution of cells with maximal protein synthesis activity also supports this view. Newly synthesized polypepides examined by gel electrophoresis show some quantitative changes during the ascites cell cycle. The polysomal distribution of total and newly synthesized poly(A)-containing RNA was examined in cell cycle enriched fractions. The results suggest a small shift in mRNA from the non-polysomal to the polysomal region of a sucrose gradient in cells that are smaller than those in S phase (presumably G1 phase cells). There is also a substantial change in the population of non-polysomal mRNA detected by translation in vitro. In this case however, cells smaller than those in S phase (presumably G1 phase cells) contain the limited population of abundant mRNAs, while these mRNAs are absent or present in reduced amounts in the presumed G2 phase cells. (no Refs)

15. METHOTREXATE RESISTANT HUMAN KB CELLS: SIZE HETEROGENEITY OF DIHYDROFOLATE REDUCTASE RELATED RNAS AND EFFECT OF METHOTREXATE ON DIHYDROFOLATE REDUCTASE ACTIVITY (MEETING ABSTRACT).

Domin BA, Bastow KF, Grill SP, Cheng YC
Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27514
Fed Proc; 41(3):1052 1982

A cloned subline of human cell variants derived from KB cells (KB/6b), 6500-fold resistant to methotrexate (MTS), exhibited a stable 40-fold elevation of the enzyme dihydrofolate reductase (DHFR) in the absence of the drug. No differences were detected between the enzyme from resistant and parental cells. Four molecular weight species of cytoplasmic RNA were identified, 4100, 1300, 990, and 790 nucleotides in length. These RNA species were enriched by chromatography on a poly (dT) affinity column and were also detected in RNA purified from polysomes. All species have translation capability in vitro. DHFR levels in these cells were dependent on the presence of MTX (methotrexate), increasing an addition 5-fold when the drug was present in the media. This increase was MTX concentration dependent and was freely reversible. The half-life of the enzyme in these cells was the same in the presence or absence of MTX, thus eliminating enzyme stabilization as being responsible for the modulation phenomenon. Furthermore, the effect of DHFR levels by MTX was blocked by cycloheximide and was not affected by actinomycin D. These results suggest that modulation of DHFR activity by MTX occurs by some post-transcriptional mechanism. (no Refs)

16. INDUCTION OF GP-2 MESSENGER RNA IN F9 CELLS BY RETINOIC ACID AND DIBUTYRYL CYCLIC AMP (MEETING ABSTRACT).

Durkin ME, Chung AE
University of Pittsburgh, Pittsburgh, PA, 15260
Fed Proc; 41(3):683 1982

The nullipotent embryonal carcinoma cell line F9 can be induced to undergo differentiation when treated with retinoic acid and dibutyryl cyclic AMP. After 48 hours of growth in medium containing 2 x 10-7M retinoic acid and 1mM dibutyryl cyclic AMP, the synthesis of the basement membrane-related glycoproteins GP-1, GP-2 (laminin), and entactin is switched on in F9 cells. The increase of GP-2 synthesis has been demonstrated by immunoprecipitation of GP-2 from cell lysates and growth medium of induced cells. Messenger RNA was extracted from induced and uninduced cells and used to program a rabbit reticulocyte lysate in vitro translation system. When translation products directed by induced F9 RNA were immunoprecipitated with GP-2 antiserum and the immunoprecipitates analyzed by SDS (sodium dodecyl sulfate)-polyacrylamide gel electrophoresis, a band was observed which has a mobility similar to that of unglycosylated precursors of GP-2 seen in endodermal cells treated with tunicamycin. This band was not visible in the immunoprecipitates of translation products directed by uninduced F9 RNA. These results suggest that the increase in GP-2 synthesis caused by retinoic acid and dibutyryl cyclic AMP is due to an increase in translatable GP-2 mRNA (messenger RNA). (no Refs)

17. POSITIVE REGULATION OF CELLULAR TRANSCRIPTS BY SV40 LARGE T-ANTIGEN (MEETING ABSTRACT).

Schutzbank T, Robinson R, Levine AJ

Department of Microbiology, State University of New York at Stony Brook, Stony Brook, NY

Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :A22 1982

Eleven c-DNA clones were obtained from a library of mRNAs derived from SV40 transformed mouse cells. Three of these cloned c-DNAs were complementary to transcripts whose steady state levels were 200 or more fold higher in SV3T3 cells compared to 3T3 cells; SV40tsA58 and Sv40tsA7 transformed mouse cells at 32 C compared to 39 C and in SV40 induced mouse tumor tissue compared to mouse liver tissue. Northern hybridization analysis of these transcripts indicates that some of these c-DNA clones are complementary to more than one RNA and that the levels of some of these multiple RNA species can be differentially regulated by SV40 large T-antigen. These experiments demonstrate that the SV40 large T-antigen can modulate up the levels of cellular m-RNA in transformed cells. (no Refs)

STRUCTURE AND LEVELS OF TRANSFER RNA

18. PATTERN OF ISOACCEPTING TRANSFER RNAS COMMON TO 26 PATIENTS WITH HODGKIN'S DISEASE.

Murphy TL, Cooper IA
(c/o Cooper) Hematology Res. Unit, Cancer Inst., 481 Little Lonsdale St., Melbourne 3000, Australia
Cancer Res; 42(9):3887-3891 1982

The elution profiles of aminoacyl transfer RNAs from Hodgkin's tumors have been compared with the corresponding patterns from normal splenic tissue. Aminohexyl-Sepharose and reversed-phase 5 chromatography have been used in the fractionation studies. Three peaks of acceptor activity have been observed in phenylalanyl, histidyl, aspartyl, and asparaginyl transfer RNAs. A second peak was shown in the case of tyrosyl and methionyl transfer RNAs. Seryl transfer RNA showed no change in elution profile; namely, a single species was observed in both normal and tumor transfer RNAs. These observations are confirmation that Hodgkin's disease is a malignant disease. The uniformity of the extra species of tRNA suggests that there is a commonly occurring aberration in the cell of origin of the Hodgkin's tumor. (Author abstract) (22 Refs)

19. ORIGIN AND FORMATION OF 1,7-DIMETHYLGUANOSINE IN TRNA CHEMICAL AND ENZYMATIC METHYLATION.

Kanduc D
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Biochim Biophys Acta; 697(3):336-343 1982

The tRNA chemical methylation: (1) 1,7-Dimethylguanosine was found in in vivo methylated tRNA from liver and kidney of rat after exposure to a low dose of dimethylnitrosamine (4 mg/kg body weight). (2) At 4 h after dimethylnitrosamine administration, the 1,7-dimethylguanosine:7-methylguanine ratio (product ratio) for liver and kidney tRNA was 0.017 and 0.091, respectively. At 24 h after dimethylnitrosamine administration, the product ratio was lower in both hepatic and renal tRNA. (3) When dimethylnitrosamine was given in four separate daily injections, the product ratio in hepatic tRNA 4 h after the last dose was the same as for the same total dose given by a single injection, but in renal tRNA it was lower. No dialkyl compound was found in liver and kidney tRNA 24 h after the last multiple injection. tRNA enzymatic methylation: (1) Base analyses of Escherichia coli B tRNA methylated in vitro, by using S-adenosylmethionine as physiological methyl donor and enzyme preparations from liver and kidney of normal rat, indicated that 1,7-dimethylguanosine was also a product of enzymatic methylation. (2) The amount of 1,7-dimethylguanosine formed by kidney enzyme preparation was 3x that produced by the liver extract. (3) A second type of enzymatic methylation assay where chemically methylated tRNA was used as substrate indicated that the 7-methylguanine residues in the nucleic acid are not the substrate of the methylase activity forming the 1,7-dimethylguanosine moieties. Analogous data were obtained for the origin of 1,7-dimethylguanosine residues in tRNA chemical methylation by dimethyl sulfate. (Author abstract) (30 Refs)

20. PUTATIVE TUMOR PROMOTER RESPONSE IN CULTURED HUMAN DIPLOID CELLS (MEETING ABSTRACT).

Trewyn RW, Gatz HB, Davakis LA, Elliott MS
Ohio State University, Columbus, OH, 43210
Proc Am Assoc Cancer Res; 23:405 1982

Investigations of the role of altered RNA metabolism in carcinogenesis have dictated the need for a human cell culture model to study the stages subsequent to initiation. By proper supplementation of the culture medium to optimize for changes in tRNA modification, carcinogen-initiated human skin cells exhibit a 3 to 4-fold increase in saturation density when exposed continuously to the tumor promoter phorbol 12,13-didecanoate (PDD). The increase in saturation density promoted by PDD does not require carcinogen initiation, but an active phorbol ester tumor promoter is required. Treatment of normal diploid cells for only 6 population doublings with PDD gives a significant increase in saturation density, whereas treatment with the inactive analog 4alpha-phorbol 12,13-didecanoate (4alpha-PDD), actually decreases the saturation density somewhat. For promotion of growth in soft agar, beta-naphthylamine-initated human cells appear to require the continuous presence of PDD. In this case, exposure to PDD is started 1 to 2 population doublings after carcinogen treatment. The human cells exposed to PDD exhibit aberrant t(transfer)RNA methyltransferase activity, and the tRNA isolated from these cells is hypomodified for quenine [7-(3,4-trans-4,5-cis-dihydroxy-1-cyclopenten-3 ylaminomethyl)-7-deazaguanine], a serum-derived purine. Similar tRNA changes are not promoted by 4alpha-PDD. (no Refs)

CHARACTERIZATION OF ENZYMES INVOLVED IN RNA SYNTHESIS, MODIFICATION AND DEGRADATION

21. ALTERATION IN DNA-DEPENDENT RNA POLYMERASE ACTIVITY BY RETINOIDS (MEETING ABSTRACT).

Mehta RG, Cerny WL, Moon RC
Life Science Division, Illinois Institute of Technology, Chicago, IL, 60616
Proc Am Assoc Cancer Res; 23:82 1982

Although the inhibitory effect of retinoids against chemically-induced mammary carcinogenesis in rats is well established, very little is known about the mechanism through which these effects are mediated. Earlier we reported the presence of retinoic acid binding proteins in the cytosol (cRABP) of carcinogen-induced mammary tumors. These components sedimented in the 2S region when analyzed by sucrose density gradient centrifugation. Furthermore, under appropriate conditions retinoic acid bound cRABP complex interacts with nuclei isolated from these tumors; RABP isolated from nuclei also sedimented as a 2S component. We now have extended these studies to determine if the mammary tumor RABP has any functional role in alteration of DNA dependent RNA polymerase activity in the nuclei. RNA polymerase activity was measured as incorporation of [3H]uridine monophosphate into trichloroacetic acid precipitable material. Cytosol containing 3.7pmoles of RA-cRABP complex (130ug protein), preformed by incubating 1uM unlabeled retinoic acid with tumor cytosol at 4C for 16 hr in dark, inhibited RNA polymerase I activity in mammary tumor nuclei by 35%. Under similar conditions, 1uM unbound RA had no effect. Mammary tumor nuclei which were incubated with cytosol containing RA-cRABP complex for 30 min at 25C also reduced Mg dependent RNA polymerase activity by over 70% compared to the nuclei preincubated with buffer under identical conditions. There was no significant influence of the RABP complex on Mn dependent RNA polymerase activity. (no Refs)

22. ESTROPHILIN LEVELS AND RNA POLYMERASE ACTIVITY IN 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA)-INDUCED MAMMARY TUMORS IN RATS (MEETING ABSTRACT).

Mohla S, Hunter JB
Howard University Cancer Center, College of Medicine, Washington, DC, 20060
Proc Am Assoc Cancer Res; 23:944 1982

Approx 60% of breast cancer patients have estrophilin (ER) of which two thirds respond favorably to hormonal therapy. Estrogens act on their target tissues by interacting with followed by translocation of the ER complex into the nucleus, resulting in increased RNA synthesis as evidenced by increased RNA polymerase activity. Using DMBA-induced mammary tumors in rats, experiments were designed to see whether RNA polymerase activity of isolated tumor nuclei may be related to their cytoplasmic ER levels. Mammary tumors were induced by a single intragastric feeding of 20 mg DMBA in 2.0 ml peanut oil. Mammary tumors were analyzed for ER using dextran coated charcoal or sucrose density gradient methods and tumor nuclei were analyzed for RNA polymerase (alpha-amanitin resistant) activity as described. A value of greater than 10 fmoles/mg protein was considered ER positive. The results indicate comparatively lower RNA polymerase activities in ER positive compared to ER negative tumor nuclei: (a) 77% (10/13) of ER positive and only 17% (1/6) of ER negative tumors exhibited low RNA polymerase activity (less than 200 pmoles 3H-UMP (uridine monophosphate)/mg DNA), (b) the incorporation of 3H-AMP or 3H-GMP (guanosine monophosphate) into RNA was also lower in ER positive tumors than in ER negative tumors. The results indicate significant correlation between ER levels and RNA synthesis and suggest additional biochemical parameters to distinguish between hormone dependent from independent tumors. The possible clinical implications of these data remain to be elucidated. (no Refs)

OTHER RELATED STUDIES

23. REGULATORY MECHANISMS IN MAMMALIAN EMBRYOGENESIS: CONTROL OF EXPRESSION OF SIMIAN VIRUS 40, HISTOCOMPATIBILITY AND BETA-2 MICROGLOBULIN GENES IN DNA- TRANSFORMED MURINE TERATOCARCINOMA CELLS.

Linnenbach AJ
University of Pennsylvania, Philadelphia, PA
Diss Abstr Int [B]; 42(6):2229-B 1981

Teratocarcinoma cells, the malignant, pluripotent stem cell of murine teratomas, have proved to be a fruitful model for the study of differentiation. We have constructed by transformation the thymidine kinase deficient F9 cell, with a selectable pBR322/HSV-1 tk/SV40 recombinant DNA, an F9 teratocarcinoma stem cell line, 12-1, which stably carries one copy per cell of the tripartite plasmid in a chromosomal site. Like its parental teratocarcinoma stem cell, the 12-1 line (1) expresses stage specific embryonic antigen-1 (SSEA-1) (2) does not express H-2 or beta-2 microglobulin, (3) does not express SV40 T-antigen, and (4) has retained the ability to differentiate in the presence of retinoic acid. The differentiated cells no longer express SSEA-1 while acquiring the H-2, beta-2 and SV40 T-antigens. The organization of the SV40 genome and its expression at the RNA and protein levels has been compared in 12-1 stem cells and a differentiated daughter cell, 12-1a, and the analysis indicates that while SV40 mRNA species are present and apparently processed identically in the two cell types, SV40 early proteins are not detected in stem cells by immunofluorescence or immunoprecipitation, indicating that regulation of expression of these proteins in stem cells is a post-transcriptional event. The differential expression of H-2 antigen, and beta-2 microglobulin in the same stem and differentiated cells is, however, due to a lack of transcription of these genes in stem cells. Thus, expression of specific genes during differentiation in murine teratocarcinoma cells, and by analogy in early mouse embryos, can be regulated by at least two different mechanisms. (no Refs)

24. THE VIRION RNA SPECIES OF THE KIRSTEN MURINE SARCOMA-LEUKEMIA VIRUS COMPLEX RELEASED FROM A CLONALLY RELATED SERIES OF MOUSE CELLS.

Clewley JP, Avery RJ
Dept. Biological Sciences, Univ. Warwick, Coventry, CV4 7AL, England
Arch Virol; 72(1/2):35-46 1982

We have characterized the virion RNA species of Kirsten sarcoma (KiSV) and Kirsten leukemia (KiLV) viruses released from a clonally related series of mouse cells (14). We have identified the KiLV and KiSV genome RNAs. In addition to the viral RNA species we find large amounts of a virus-like RNA (VL30 RNA), which is heterogeneous and shows variability in its expression. The amount of VL30 RNA in virions does not correlate with the state of transformation of the cells releasing the virus or the ability of the virus to transform other cells. Characterization of RNA rescued from non-producer cells has revealed a sarcoma virus (KiSVCB3) with an oligonucleotide fingerprint different from that of a standard KiSV RNA, suggesting that it has lost some viral sequences. The oligonucleotide fingerprints of KiLV and VL30 RNAs are distinct from each other and from those reported for other murine leukemia virus RNAs. (Author abstract) (21 Refs)

25. STUDIES ON THE ABILITY OF THYMIDINE TO MODIFY THE CHEMOTHERAPEUTIC ACTIVITY AND METABOLISM OF 5-FLUOROURACIL AND 1-BETA-D-ARABINOFURANOSYLCYTOSINE IN RATS AND MICE.

Danhauser LL
State University of New York at Buffalo, Buffalo, NY
Diss Abstr Int [B]; 42(9):3647-B 1982

The therapeutic efficacy of equitoxic doses of concurrent thymidine (TdR) and 5-fluorouracil (FU) vs FU alone was studied in rats and mice bearing transplantable colon tumors. Under the conditions employed, TdR did not significantly alter the antitumor activity of FU in rats or mice. The toxicity of FU, however, could be enhanced in vivo by co-administration of TdR. Analysis of rat plasma showed increased circulating levels of TdR and thymine (T) and reduced levels of deoxycytidine (CdR) during TdR infusion. TdR effects on FU metabolism included: (1) TdR infusion reduced systemic FU catabolism and increased circulating levels of FU relative to FU alone; (2) TdR did not alter the incorporation of FU into tumor RNA, but appeared to enhance FU incorporation into the RNA of normal tissues; (3) tumor 5-fluorodeoxyuridylate (FdUMP) levels were reduced by TdR; however, thymidylate synthetase inhibition by FdUMP was complete using FU or FU and TdR. Because TdR infusion reduced rat plasma CdR levels, the effect of TdR on 1-beta-D-arabinofuranosylcytosine (ara-C) activity in rats was examined. TdR enhanced ara-C toxicity, the magnitude depending upon the treatment schedule. The best tumor growth inhibition resulted from infusion of TdR prior to ara-C. Whereas TdR increased ara-C triphosphatase (ara-CTP) levels over control in both tumor and host tissues, 3-6 hrs post-TdR, ara-C levels were elevated only in the tumor. Consequently, the toxicity but not the antitumor activity of ara-C could be reduced by delayed infusion of ara-C following TdR. These data provide evidence for in vivo modulation of a metabolite, CdR (presumably an index of intracellular CdR metabolism), by another metabolite, TdR, resulting in augmentation of the effects of an antimetabolite, ara-C. (no Refs)

26. NUCLEOSIDES AND CANCER (MEETING ABSTRACT).

Lin W, McCoy JR, MacKenzie JW, Clark I
CMDNJ-Rutgers Medical School, Piscatway, NJ, 08854
Fed Proc; 41(3):927 1982

Increased urinary excretion of modified nucleosides and bases, primarily derived from tRNA, is a common feature of mammals with neoplasms. The present study compares the patterns of modified urinary nucleosides and bases of rats with aflatoxin B1 induced hepatomas and dimethylnitrosoamine induced nephroblastomas. Both carcinogens caused marked increases in the same modified nucleosides and bases. However, the quantitative profiles of these excretory products were significantly different. Increased growth of the neoplasms was accompanied by further elevation in levels of these metabolites. Although increased turnover of tRNA, and not cell death, is believed to be the primary reason for the elevated levels in the urine, the data suggest that increased turnover of mRNA and perhaps rRNA are also contributing factors. Specific activities of tRNA from tumor tissue of rats dosed with 14CH3 methionine showed increased incorporation of methyl groups at 4 and 24 hours. The results suggest that the levels and quantitative profiles of urinary modified nucleosides may be useful in the diagnosis of cancer. (no Refs)

27. EFFECTS OF OLIVACINE ON THE METABOLISM OF PROTEINS AND NUCLEIC ACIDS IN ESCHERICHIA COLI.

Touaty P, Simon M
Laboratoire d'Enzymologie Microbienne, C.N.R.S., 91190 Gif-sur-Yvette, France
Biochim Biophys Acta; 697(3):313-321 1982

Olivacine, a semi-synthetic isomer of ellipticine, interferes with the growth of Escherichia coli. Investigation of the effects of graded concentration shows that, in vivo, the synthesis of overall proteins is markedly more sensitive to low concentrations than is the synthesis of RNA and DNA, respectively. Furthermore, at moderate concentrations, olivacine is much more inhibitory to the synthesis of cytoplasmic proteins than to that of envelope proteins. At lethal concentration (10(-4)) all macromolecular syntheses are inhibited, DNA synthesis, however, to a lower extent. Olivacine blocks the synthesis of polyribonucleotide and polypeptide chains at the elongation step. The resulting nascent products of both transcription and translation are unstable, whereas completed RNA molecules are partially stabilized in the presence of the drug. (Author abstract) (20 Refs)

28. INHIBITION OF TRANSLATION OF SATELLITE TOBACCO NECROSIS VIRUS (STNV) RNA MODIFIED BY (+/-)-7BETA,8ALPHA-DIHYDROXY-9ALPHA,10ALPHA-EPOXY 7,8,9. 10-TETRAHYDROBENZO[A]PYRENE (BPDE) IN A WHEAT GERM CELL-FREE SYSTEM (MEETING ABSTRACT).

Haas R, Grunberger D
Colubmia University, Institute of Cancer Research, New York, NY, 10032
Proc Am Assoc Cancer Res; 23:250 1982

A previous study from this laboratory showed that BPDE modification of rabbit globin mRNA results in inhibition of translational initiation. It was of interest to explore the possibility that modification of the 5' cap structure was responsible for this inhibition. Therefore, we reacted the naturally non-capped mRNA from STNV with BPDE and translated it in a wheat germ cell-free system. The extent of modification was 1.3 and 2.9 BPDE residues/molecule. High performance liquid chromatography of the modified nucleosides from enzymatically hydrolyzed STNV RNA reveals that more than 90% of the nucleoside adducts were substituted at the exocyclic amino group of guanosine. The translational ability of the modified STNV, measured by incorporation of [14C] amino acids into acid-precipitabie polypeptides is inhibited by about 60%. Polyacrylamide gel electrophoretic analyses of the translation products indicate that only full-length coat proteins are synthesized but with the carcinogen-modified STNV the amount is reduced. On the other hand, 80S initiation complex formation was not inhibited as measured by binding of the BPDE-modified STNV to ribosomes and followed by glycerol gradient centrifugation. Under these conditions, aurintricarboxylic acid completely inhibits 80S initiation complex formation in the presence of both modified and native STNV. (no Refs)

29. ALKYLATION OF GUANINE BY N-PROPYLDIAZONIUM ION. MOLECULARITY IS A FUNCTION OF BOTH NUCLEOPHILE AND ELECTROPHILE (MEETING ABSTRACT).

Scribner JD, Ford GP
Pacific Northwest Research Foundation, Seattle, WA, 98104
Proc Am Assoc Cancer Res; 23:235 1982

It has been reported that n-propyldiazonium ion alkylates N-7 of guanine in rat liver DNA to give 7-n-propylguanine, evidence that this ion reacts bimolecularly, without the formation of carbonium ions. It appeared to us, however, that N-7 of guanine may act as a highly nucleophilic trapping agent, and that weaker nucleophiles, such as O6, would react only with the less selective free carbonium ion. This was tested in vitro and in vivo, and theoretical studies undertaken to explain the results. Treatment of guanosine in water with n-propylnitrosourea gave a 3:1 ratio of O6/7 alkylation products. The only detectable O6 adduct was O(6)-isopropylguanosine, while the only detectable N-7 adduct was 7-n-propylguanosine. (3H)-Di-n-propylnitrosamine was injected into rats, which were sacrificed 12 hr later, and the liver DNA and RNA isolated. Portions of the RNA were digested enzymatically or with 1N HCl. The enzyme digest contained standard adducts, which were reisolated by ethyl acetate extraction and thin layer chromatography. After rechromatography of the standards, the specific activity of O(6)-i-propylguanosine was 7x higher than that of O(6)-n-propylguanosine. The acid digest was chromatographed directly with standards on a high resolution ion-exchange column, with a result like that of Park, et al. Thus we have shown that, while N-7 traps the n-propyldiazonium ion in a bimolecular reaction, O6 reacts predominantly in a manner which permits prior decomposition and rearrangement of the alkyl group, ie, alkylation of O6 has the properties of a unimolecular reaction. (1 Ref)

30. PURINE STARVATION: THE ROLE OF GUANINE RIBONUCLEOTIDE DEPLETION (MEETING ABSTRACT).

Cohen MB, Sadee W
University of California, San Francisco, School of Pharmacy, San Francisco, CA, 94143
Proc Am Assoc Cancer Res; 23:851 1982

The importance of the depletion of guanine nucleotides in cellular toxicity was compared to that of adenine nucleotides following the inhibition of early de novo purine biosynthesis in the mouse T lymphoma (S-49) cell line. Early de novo purine biosynthesis was blocked with 6-methyl-mercaptopurine riboside (6MMPR), while adenine and guanine nucleotide biosyntheses were individually inhibited using alanosine and mycophenolic acid (MA), respectively. The effects of a 3 h incubation with either 2.0 uM 6MMPR or 1.2 uM MA were similar; a partial reduction in RNA synthesis and a dramatic inhibition of DNA synthesis. However, a 3 h incubation with 3.75 uM alanosine did not affect either DNA or RNA synthesis, although the concentration of ATP was reduced to a lower level than that caused by 6MMPR. We also compared the ability of exogenous sources of guanine or adenine nucleotides to return GTP (guanosine triphosphate) and/or ATP levels to normal with their ability to reestablish DNA synthesis in cells treated with 2.0 uM 6MMPR for 3 h. Resumption of DNA synthesis was dependent on the return of guanine, but not of adenine nucleotide levels to normal. These results suggest that a process of cells which uses guanine nucleotides is compromised before that of adenine nucleotides when de novo purine biosynthesis is inhibited. We previously found that the depletion of guanine ribonucleotides rather than guanine deoxyribonucleotides is associated with toxicity when guanine nucleotide biosynthesis is inhibited and that the depletion is associated with the inhibition of DNA synthesis. (1 Ref)

31. THE MECHANISM OF ACTION OF FAGARONINE, A NOVEL TUMOR INHIBITOR (MEETING ABSTRACT).

Pezzuto JM, Honig GR, Antosiak SK, Farnsworth NR
University of Illinois at the Medical Center, Chicago, IL, 60612
Proc Am Assoc Cancer Res; 23:812 1982

Fagaronine (2-hydroxy-3,8,9-trimethoxy-5-methyl benzo[c]phenanthridine) is an active antileukemic agent orginally isolated in our laboratory from the roots of Fagara zanthoxyloides. The present studies are concerned with its mechanism of action. Upon admixture with DNA, a significant hypsochromic shift was noted in the absorption spectrum of fagaronine with a maximum at 395 nm. The magnitude of the shift was dependent upon the concentration of DNA, and clear isosbestic points suggest intercalative binding. Similar spectra were obtained with poiy(dA-dT): poly(dA-dT) or poly(dG): poly(dC) indicating the interaction of fagaronine with these species, and this was confirmed by experiments involving gel filtration column chromatography. Fagaronine can also bind to ribonucleic acids containing double-stranded regions such as tRNA, poly(A): poly(U), poly(G): poly(C), and poly(I): poly (C), but isosbestic points were not discernable. Conversely, poly(A), poly(U), poly(G), poly(C), poly(I), AMP, UMP (uridine monophosphate), GMP (guanosine monophosphate), or CMP (cytidine monophosphate) can not effectively interact with fagaronine as judged by the absorption spectra. Additionally, the mutagenic potential of fagaronine was examined utilizing Salmonella typhimurium strain TM677. Fagaronine is not mutagenic. It is bactericidal, however, and this activity is greatly enhanced upon addition of a liver homogenate derived from Aroclor 1254 pretreated rats, and NADPH. N-Demethylfagaronine, a potential metabolite, is also not mutagenic. Moreover, it is not bactericidal and the addition of DNA does not significantly alter the absorption spectra. The results suggest that fagaronine functions by virtue of interaction with double-stranded nucleic acids, and the guanidinium functionality is required for binding. The active antitumor principle is probably a metabolite of fagaronine, and the chemical nature of this species is currently under investigation. (no Refs)

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